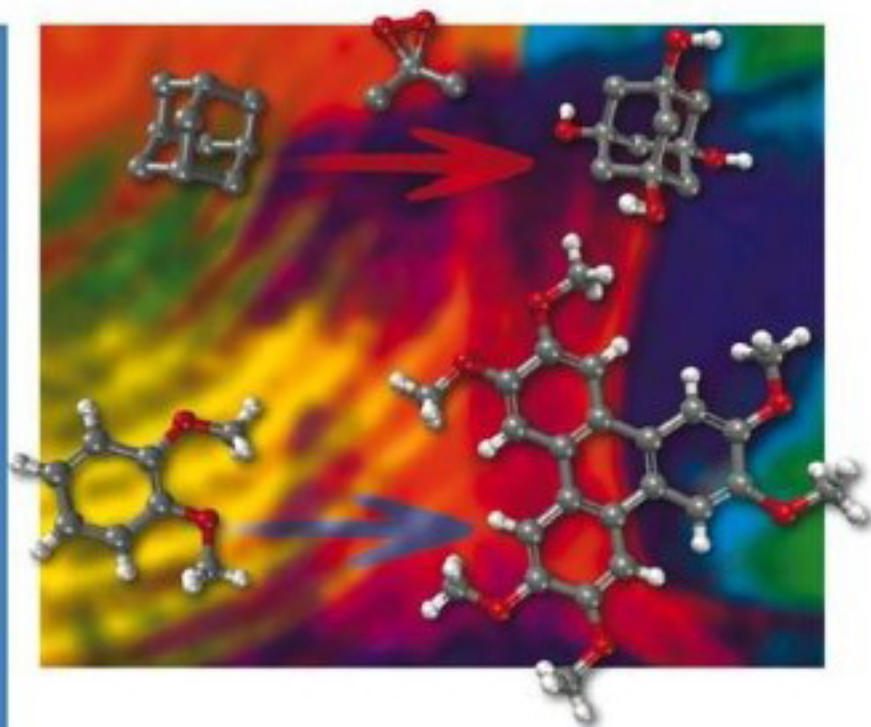


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Handbook of C–H Transformations

Applications in Organic Synthesis



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Gerald Dyker



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Preface

The direct transformation of C-H bonds is a fundamental task in organic synthesis, regularly facing reactivity and selectivity problems but simultaneously promising substantial benefits. The intention of this handbook, written by renowned authors who have contributed substantially to this research area, is to present, very concisely within its 66 sections, the whole range of modern methods for C-H-transformation.

Most of the sections follow a general concept and are therefore divided into five parts which cover the most important features of the reaction in focus. "Introduction and Fundamental Examples" gives general information about the reaction, especially the scientific background and related reactions. This part also includes reactions which might be important to understanding although not necessarily of preparative value. "Mechanism" presents current mechanistic considerations, eventually including critical remarks. "Scope and Limitations" concentrates on examples which lead to interesting structures, usually with yields in excess of 50%. "Experimental" presents instructive, comprehensible examples, including work-up procedures. Information about appropriate methods for monitoring the reaction (TLC data or diagnostic NMR spectroscopy) are also given. If a special catalyst is needed, the procedure for its synthesis is also included. "References and Notes", of course, leads to significant publications where further details are available.

You may notice that this preface is as concise as the contents of this handbook. Nevertheless, as editor I should not forget to thank all authors and the team from Wiley-VCH, who made this project possible. The transformation of C-H bonds is certainly one of the most important fields of research in preparative organic chemistry; let us hope this handbook will further motivate research, simultaneously accelerating the change from new developments to established synthetic tools.

Gerald Dyker

Bochum, April 2005

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General

1

What is C–H Bond Activation?

Bengü Sezen and Dalibor Sames

1.1

Introduction

The possibility of direct introduction of a new functionality (or a new C–C bond) via direct C–H bond transformation is a highly attractive strategy in covalent synthesis, owing to the ubiquitous nature of C–H bonds in organic substances. The range of substrates is virtually unlimited, including hydrocarbons (lower alkanes, arenes, and polyarenes), complex organic compounds of small molecular weight, and synthetic and biological polymers. Consequently, selective C–H bond functionalization has long stood as a highly desirable goal. The introduction of transition metals to the repertoire of reagents unlocked entirely new opportunities in this area. As such, novel reactions have been discovered and the term “C–H bond activation” has been coined and used to describe certain C–H cleaving processes, initially in the context of saturated hydrocarbons. With time this term has become popular, if not fashionable, and its frequent and liberal usage has led to some uncertainty about its definition and meaning. Complex organic substrates contain a plethora of C–H bonds of different acidity and reactivity, and consequently many mechanistic modes exist for an overall C–H functionalization process (e.g. radical, electrophilic substitution, deprotonation, metal insertion).

Naturally, the question of which processes can be described as “C–H bond activation” arose. After numerous discussions with colleagues in the broad chemical community, we felt compelled to provide some thoughts on this topic, including a historical perspective.

1.2

Activation or “Activation”

In lay language, “activation” means making an object or a person active. A number of fields of science and engineering have adopted this term to describe various processes and phenomena (e.g. regeneration of inorganic catalyst, transformation of inactive enzyme to an active form, excitation by heating or irradiation) [1]. In

the context of chemical reactions, “activation of a substrate” or “activation of a bond” refers to, in a most general sense, any process or phenomenon by which the reactivity of a substrate or a bond is increased. Thus, this represents a rather open term and as such is used by the chemical community in many different ways and contexts; for instance, activation of bonds by substituents (cf. activated C–H bonds in malonate esters) or activation of bonds by formation of a discrete intermediate between the substrate and a reagent (cf. alkene activation by Lewis acids). Although distinction between “activation” and “reaction” can in principle be made, “bond activation” is frequently equated with bond cleavage. For instance, activation of strong bonds (C–H, C–C, C–F) is often understood as cleavage of these bonds with transition metal reagents. Similarly, “nitrogen activation” describes a variety of processes for reduction of N_2 to hydrazine or ammonia.

In this light, we can appreciate the wide spectrum of interpretations and uses of this terminology. To bring some clarity to our discussion, we first need to make a clear distinction between “activation” and “reaction”. In harmony with the general understanding of the term “activation”, “*bond activation*” should refer to any chemical process which increases the reactivity of a bond in question (“general definition”) [2]. On the other hand, bond-cleaving processes should be labeled by a separate term, for instance “*bond transformation*”. We should emphasize that both of these terms, used in this general sense, cast no limits on the actual activation or reaction mechanism.

Nevertheless, in addition to this general understanding of the term, “bond activation” has acquired specific meaning in various subdisciplines. Most notably, “C–H bond activation” is frequently used as an organometallic term to describe certain metal-mediated processes (“organometallic definition”). Before we address this inconsistency, let us first elucidate the origin and historical context of “C–H bond activation” as an organometallic term.

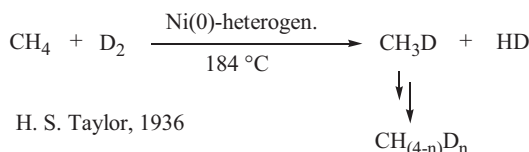
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The Origin and Historical Context of the “Organometallic Definition”

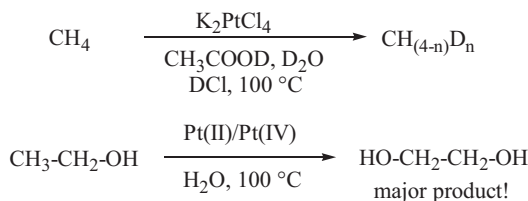
One of the early uses of the “C–H bond activation” term appeared in the chemical literature in 1936 to describe the H–D exchange in methane catalyzed by a heterogeneous Ni^0 catalyst (Scheme 1) [3]. Although no definition of the term was provided, this work implied that a new mode of chemical reactivity was operative at the metal surface, enabling cleavage of alkane C–H bonds. With some insight, an analogy between this new process and cleavage of a hydrogen molecule on hydrogenation surfaces was proposed.

A few decades later in 1968, Halpern formulated the need for new approaches to the activation of C–H bonds with a particular focus on saturated hydrocarbons. C–H bond activation, equated with “dissociation of carbon–hydrogen bonds by metal complexes”, was identified as one of the most important challenges in catalysis [4]. Perhaps the most influential discovery in this area was made in the late 1960s by Hodges and Garnett, who demonstrated that a *homogeneous* aqueous so-

lution of platinum(II) salts catalyzed deuteration of arenes and alkanes [5]. Subsequently, Shilov extended this work by using mixtures of platinum(II) and platinum(IV) salts to achieve hydroxylation and chlorination of alkanes, including methane (Scheme 2) [6]. This work inspired numerous mechanistic studies which established an alkylplatinum species as a reasonable intermediate. Most notably, unusual chemo-selectivity was observed, because rate constants for oxidation of an unactivated methyl group were occasionally greater than those for the oxidation of an alcohol (Scheme 2) [7]. Clearly, a new reactivity mode, other than radical or ionic substitution, had been discovered and the term “activation of saturated hydrocarbons” was used.



Scheme 1

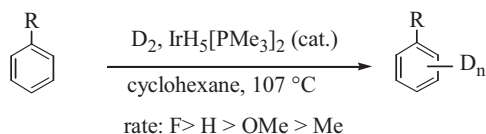


Garnett-Shilov, 1969

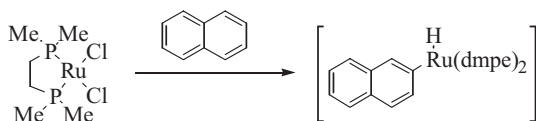
Scheme 2

Transition metal complexes have also unlocked new mechanistic possibilities for cleaving arene C–H bonds. Hydrogen–deuterium exchange at the benzene nucleus, catalyzed by homogeneous metal hydride complexes, was demonstrated by Parshall (Scheme 3) [8]. Interestingly, it was observed that electron-deficient arenes underwent the labeling reaction at faster rates. These results (reaction rates and regioselectivity) were inconsistent with electrophilic substitution; rather, the metal complexes had nucleophile-like properties which pointed to a new mechanism. The intermediacy of arene–metal hydride species, similar to those observed earlier by Chatt and Davidson [9], was proposed (Scheme 3). By analogy with the reaction of alkanes, these new processes were described as “C–H bond activation”, to distinguish them from electrophilic metalation and electrophilic substitution reactions.

Thus, the historical context reveals that the term “C–H bond activation” was introduced with a clear purpose to distinguish metal-mediated C–H cleavage from traditional radical and ionic substitution, and as such was essentially a mechanistic term [8]. As a result we may formulate the “organometallic definition”: *the term “C–H bond activation” refers to the formation of a complex wherein the C–H bond*



G. W. Parshall, 1972



J. Chatt and J. M. Davidson, 1965

Scheme 3

interacts directly with the metal reagent or catalyst. These complexes often afford a C–M intermediate in the absence of free radical or ionic intermediates.

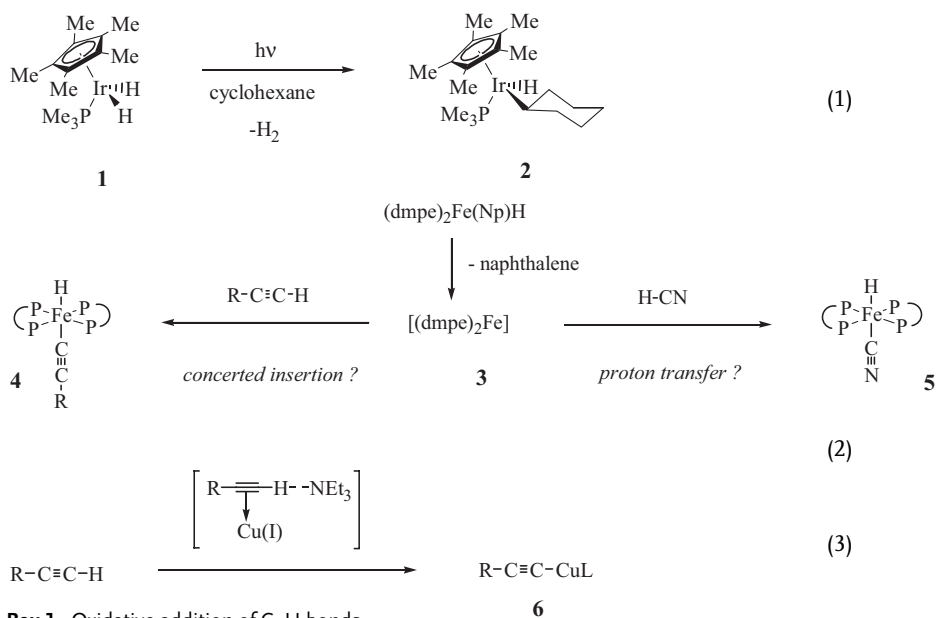
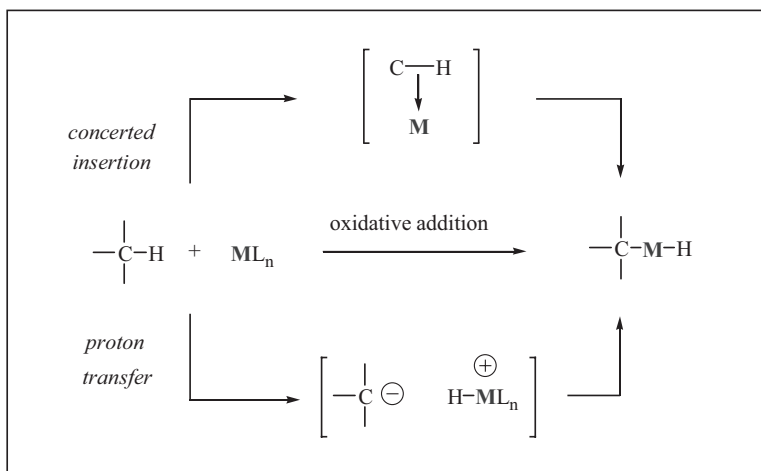
We believe this definition captures the essence of numerous proposals in the organometallic literature [10]. Indeed, the term “C–H bond activation” is used routinely to differentiate, for instance, between oxidative addition pathways and deprotonation [11].

1.4

What Do We Do With Two Definitions?

Equation (1) depicts an early example of an intermolecular addition of an alkane C–H bond to a low valent transition metal complex [12]. Mechanistic investigations provided strong evidence that these reactions occur via concerted oxidative addition wherein the metal “activates” the C–H bond directly by formation of the dative bond, followed by formation of an alkylmetal hydride as the product (Box 1). Considering the overall low reactivity of alkanes, transition metals were able to “make the C–H bonds more reactive” or “activate” them via a new process. Many in the modern organometallic community equated “C–H bond activation” with the concerted oxidative addition mechanism [10b,c].

Strictly speaking, however, in addition to the concerted pathway, oxidative addition can also proceed via radical or ionic mechanisms [13]. Although these alternatives are less likely for alkanes (cf. Eq. 1) they must be considered with substrates containing reactive C–H bonds. For example, proton transfer is a readily available process for acidic C–H bonds (Box 1). Insertion of low valent transition metals has been reported in substrates including alkynes, ketones, and nitriles. As an example, the synthesis of iron hydride complex **5** was accomplished by treating a terminal alkyne with Fe(dmpe)₂, generated in situ (Eq. 2). This reaction, assumed to proceed via concerted oxidative addition, stands in stark contrast to deprotonation by a strong base. The label “C–H bond activation” was used to make this distinction and we may argue that it serves well as a qualitative mechanistic term.

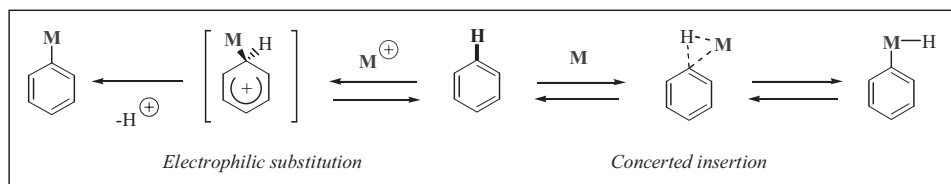


Box 1. Oxidative addition of C-H bonds.

Difficulties arise, however, when the organometallic definition is to be applied in a rigorous mechanistic sense. This point is illustrated by comparing the reactions of the iron complex in Eq. (2) with an alkyne or with HCN [14]. Although a metal hydride is the product in both reactions, a significantly faster rate was observed with HCN. This observation suggests that addition of HCN proceeds via proton transfer. Which of these processes can be described as “C-H bond activation”? According to the organometallic definition proton transfer as an ionic pro-

cess would be disqualified. What, however, if oxidative addition proceeds via proton transfer, followed by very fast ion recombination? What if a new experiment suggests that the iron metal interacts with the alkyne triple bond before a proton-transfer step? These questions are often contentious and debated issues and experimental measurements from two different laboratories may favor different mechanistic proposals. This case illustrates the types of problematic issue that arise when attempting to define “C–H bond activation” as a rigorous mechanistic term.

Furthermore, the inconsistency between the restrictive organometallic definition and the general understanding of “bond activation” will pose further problems. Let us discuss this issue in the context of a concrete example – alkyne cupration. It is thought that copper complexation and base-assisted deprotonation work in concert ultimately forming the alkynyl cuprate (Eq. 3). Thus, the proposed cupration mechanism may be viewed as a variation of the deprotonation mechanism (π -acid/base-promoted deprotonation) [15]. Experimental evidence shows that Cu^{I} salts increase the acidity of the terminal alkyne C–H bond by coordination to the π -bond [16]. Hence, it is clear that copper metal activates the alkyne C–H bond; following the organometallic definition, however, would lead to an absurd linguistic situation; i.e. copper activates the alkyne C–H bond but it is not “C–H bond activation”.



Box 2. Arene metalation. Electrophilic versus concerted insertion.

Another instructive scenario may be found when considering the metalation of arenes. There are two distinct mechanisms for the metalation of aromatic C–H bonds – electrophilic substitution and concerted oxidative addition (Box 2). The classical arene mercuriation, known for more than a century, serves to illustrate the electrophilic pathway whereas the metal hydride-catalyzed deuterium labeling of arenes document the concerted oxidative addition mechanism [8, 17]. These two processes differ both in kinetic behavior and regioselectivity and thus we may appreciate the need to differentiate these two types of process. However, the choice of “C–H bond activation” to designate only one, the oxidative addition pathway, creates a similar linguistic paradox. Indeed, it is hard to argue that the C–H bond in the cationic σ -complex is not activated.

These examples clearly illustrate that “bond activation”, whether it refers to C–H bonds or other bonds, is a poor choice for designation of certain reaction types and mechanisms.

1.5 Conclusions

The analysis of the origin and usage of the term “C–H bond activation” revealed dichotomy between the organometallic definition of this term and the general understanding of the word “activation”. As discussed in this essay, “C–H bond activation” is frequently used in the organometallic sense and indeed serves well as a qualitative mechanistic term. Although distinction between the organometallic “C–H bond activation” and general “activation” could be made (and is made intuitively by many), this is clearly degenerate and inconsistent terminology. We have, furthermore, shown that it is difficult to find a rigorous mechanistic basis for defining a “C–H bond activation” class of processes according to the organometallic definition discussed herein.

Consequently, we were faced with the task of formulating a widely acceptable and consistent definition of “bond activation”. Our research, discussions, and analyses led to a conclusion that “bond activation” should refer to a process of increasing the reactivity of a bond in question and as such encompasses an entire spectrum of possible mechanisms. Also, we argue that “activation” is not equivalent to “reaction” or, in other words, that “activation” of a bond is not the same as cleavage of a bond. For the latter process we proposed the general term “bond transformation”. It should be emphasized that both “bond activation” and “bond transformation” are general terms and, therefore, information about the reaction and mechanism category should be specified by additional descriptors (cf. C–H bond arylation via electrophilic metalation, C–H bond metalation via concerted metal insertion).

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References and Notes

- 1 (a) R. Grant, C. Grant, *Grant and Hackh's Chemical Dictionary*, 5th edn, McGraw–Hill, New York, **1987**;
(b) A. D. McNaught, A. Wilkinson, *Compendium of Chemical Terminology, IUPAC Recommendations*, 2nd edn, TSC, Cambridge, UK, **1997**; (c) *International Encyclopedia of Chemical Science*, Van Nostrand, Princeton, **1964**.
- 2 This view has previously been suggested in print. G. Dyker, J. Heiermann, M. Miura, *Adv. Synth. Catal.* **2003**, 345, 1127–1132. We also thank Professor G. Dyker for sharing his thoughts on this subject.
- 3 K. Morikawa, W. S. Benedict, H. S. Taylor, *J. Am. Chem. Soc.* **1936**, 58, 1445–1449. According to our search, the first time the phrase “activation of C–H bond” was used dates to **1929**. Incidentally, authors referred to activation of arene C–H bonds by the substituents. F. Swarts, *Recl. Trav. Chim. Pays. Bas.* **1929**, 48, 1025–1028.
- 4 J. Halpern, *Discuss. Faraday Soc.* **1968**, 46, 1–20.
- 5 R. J. Hodges, J. L. Garnett *J. Catal.* **1969**, 13, 83–98.
- 6 N. F. Gol'dshleger, M. B. Tyabin, A. E. Shilov, A. A. Shteinman, *Russ. J. Phys. Chem.* **1969**, 1222–1223.
- 7 (a) J. A. Labinger, A. M. Herring, D. K. Lyon, G. A. Luinstra, J. E. Bercaw, *Organometallics*, **1993**, 12, 895–905;
(b) A. Sen, M. A. Benvenuto, M. Lin, A. C. Hutson, N. Basickes, *J. Am. Chem. Soc.* **1994**, 116, 998–1003.
- 8 G. W. Parshall, *Acc. Chem. Res.* **1975**, 8, 113–117.
- 9 J. Chatt, J. M. Davidson, *J. Chem. Soc.* **1965**, 843–855.
- 10 (a) M. L. H. Green, D. O'Hare, *Pure Appl. Chem.* **1985**, 57, 1897–1910;
(b) R. H. Crabtree, *J. Chem. Soc., Dalton Trans.* **2001**, 2437–2450; (c) W. D. Jones, *Acc. Chem. Res.* **2003**, 36, 140–146.
- 11 (a) E. J. Hennessy, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, 125, 12084–12085; (b) C.-H. Park, V. Ryabova, I. V. Seregin, A. W. Sromek, V. Gevorgyan, *Org. Lett.* **2004**, 6, 1159–1162.
- 12 (a) A. H. Janowicz, R. G. Bergman, *J. Am. Chem. Soc.* **1982**, 104, 352–354. For other related processes:
(b) W. D. Jones, F. J. Feher, *J. Am. Chem. Soc.* **1984**, 106, 1650–1663.
- 13 (a) J. Halpern, *Acc. Chem. Res.* **1970**, 3, 386–392; (b) C. Amatore, F. Pfluger, *Organometallics*, **1990**, 9, 2276–2282.
- 14 S. D. Ittel, C. A. Tolman, A. D. English, J. P. Jesson, *J. Am. Chem. Soc.* **1978**, 100, 7577–7585.
- 15 For related zincation of alkynes:
D. E. Frantz, R. Fässler, C. S. Tomooka, E. M. Carreira, *Acc. Chem. Res.* **2000**, 33, 373–381.
- 16 J. G. Hefner, P. M. Zizelman, L. D. Durfee, G. S. Lewandos, *J. Organomet. Chem.* **1984**, 260, 369–380.
- 17 Similarly, recent computational studies suggested that the iridium-catalyzed borylation of arenes also proceeded via the insertion mechanism. H. Tamura, H. Yamazaki, H. Sato, S. Sakaki, *J. Am. Chem. Soc.* **2003**, 125, 16114–16126 and references therein.

2

C–H Transformation in Industrial Processes

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2.1

Introduction

The general aim of C–H transformation is to introduce groups with a higher complexity to hydrocarbon structures. Industrial processes therefore usually involve transformation of C–H groups starting from simple molecules. The reactions employed are selective oxidation, substitution (radical, electrophilic), nitration, ammoxidation, and sulfonation. The functionalized molecules are then further converted to more valuable products and intermediates by different reaction pathways. The latter often comprise further steps of C–H-activation.

This chapter can only give a brief summary of the many reactions used for C–H transformation in commercial chemical processes. Further detailed information about the reactions can be found in the general literature about industrial chemistry [1–3]. A general survey of C–H transformation of alkanes, olefins, and aromatics will be given in Sections 2.2 to 2.4. In Section 2.5 the synthesis of fine chemicals will be considered separately. The production of basic chemicals, raw materials, and intermediates described in the first three sections differs significantly from the production of fine chemicals and highly functionalized products such as pharmaceuticals. The difference originates not only because of the quantity produced and reactor size but also because of the significantly different chemistry. It is therefore the aim of this chapter to summarize the main characteristics of the different reactions, i.e. to illustrate the similarities and differences and current and future needs for process development.

2.2

Alkane Activation

An overview of the main reactions and processes is given in Table 1. Functionalization of lighter hydrocarbons to basic chemicals is performed by thermal activation, oxidation, sulfoxidation, ammoxidation, and chlorination. Reactions are carried out either in the gas phase or under milder conditions in the liquid phase.

Thermal activation of light hydrocarbons, e.g. CH_4 , is used for the production of acetylene at high temperatures and extremely short residence times (Table 1, entry 1). Because of the thermodynamics and kinetics of the reaction the production of acetylene by conversion of light hydrocarbons, preferably C_1 , is conducted at temperatures above 1000°C and with extremely low residence times of less than 10 ms. The heat for the reaction is supplied by burning a part of the feedstock in a burning zone followed by a rapid quenching of the product mixture with oil or water (partial combustion processes). Various processes operating according to this basic principle are known [4, 5].

Perhaps the most important industrial reaction is the production of synthesis gas, a gas mixture containing CO and H_2 in different proportions (Table 1, entry 2). Natural gas-based processes have successfully replaced coal-based routes to synthesis gas. The desired, more valuable product generated is hydrogen. Most of the hydrogen produced (>70 %) is used in the production of ammonia and methanol and in refinery processes. The reforming reaction occurs over a heterogeneous catalyst in a fixed-bed tubular reactor. Synthesis gas is usually generated by steam reforming, first described in patents in 1912 [6], and the main carbon

Table 1. Industrial processes for C–H transformation of alkanes.

	Educt	Condition/reactant	Product
1	C_1	$T > 1000^\circ\text{C}$	Acetylene [4]
2	C_1 and higher	H_2O , O_2	Synthesis gas [6]
3	C_1	O_2/NH_3	Hydrogen cyanide [7, 8]
4	C_{2+}	$T = 750\text{--}900^\circ\text{C}$, cat.	Olefins, diolefins, aromatics [10]
5	C_4	Catalyst/ O_2	Maleic anhydride [11]
6	C_1	Cl_2	Chlorinated hydrocarbons [13, 14]
7	<i>i</i> - C_4	O_2	<i>tert</i> -Butylhydroperoxide [15]
8	Linear/cycloalkane	H_2O (H_3BO_3)	Secondary alcohols [16, 17]
9	Linear/cycloalkane	O_2	Alcohols, ketones, carboxylic acids [19]
10	<i>n</i> -Alkanes	Cl_2 , SO_2	Alkanesulfonylchlorides [18]
11	<i>n</i> -Alkanes	O_2/SO_2	Alkanesulfonic acids [18]
12	Cyclohexane	NOCl	Cyclohexanol, cyclohexanone (oxime), caprolactam [19, 20]
13	Paraffins	HNO_3	Nitro compounds
14	C_1	S	Carbon disulfide
15	<i>n</i> -Alkanes	O_2 , nutrients microorganism	Proteins

source nowadays is natural gas. Alternatively synthesis gas can be produced by partial oxidation. Partial oxidation (POX) is employed in the new generation of gas-to-liquid processes. Finally, autothermal reforming, i.e. a combination of partial oxidation and steam reforming must be mentioned. All these processes are performed at high temperatures ($>900^{\circ}\text{C}$) and high pressures (up to 15 MPa).

The direct conversion of methane with oxygen and ammonia results in the formation of hydrogen cyanide (Table 1, entry 3); the dehydration of formamide is of minor importance only. The reaction is highly endothermic and the various processes differ mainly in the method of energy supply to the reaction system. Different processes have been developed for this short-contact-time reaction, with the most important being the Andrussow process with platinum-based gauze as catalyst and a reaction temperature higher than 1000°C [7], the Degussa BMA process carried out in tube bundles with a thin layer of platinum catalyst [8], and the Shawinigan process in a fluidized bed in the absence of a metal catalyst at $T = 1500^{\circ}\text{C}$ [9].

The thermal and catalytic conversion of different hydrocarbon fractions, often with hydrotreating and other reaction steps, is characterized by a broad variety of feeds and products (Table 1, entry 4). New processes starting from natural gas are currently under development; these are mainly based on the conversion of methane into synthesis gas, further into methanol, and finally into higher hydrocarbons. These processes are mainly employed in the petrochemical industry and will not be described in detail here. Several new processes are under development and the formation of BTX aromatics from C_3/C_4 hydrocarbons employing modified zeolite catalysts is a promising example [10].

The oxidation of butane (or butylene or mixtures thereof) to maleic anhydride is a successful example of the replacement of a feedstock (in this case benzene) by a more economical one (Table 1, entry 5). Process conditions are similar to the conventional process starting from aromatics or butylene. Catalysts are based on vanadium and phosphorus oxides [11]. The reaction can be performed in multitubular fixed bed or in fluidized bed reactors. To achieve high selectivity the conversion is limited to $<20\%$ in the fixed bed reactor and the concentration of C_4 is limited to values below the explosion limit of approx. 2 mol% in the feed of fixed bed reactors. The fluidized-bed reactor can be operated above the explosion limits but the selectivity is lower than for a fixed bed process. The synthesis of maleic anhydride is also an example of the intensive process development that has occurred in recent decades. In the 1990s DuPont developed and introduced a so called cataloreactant concept on a technical scale. In this process hydrocarbons are oxidized by a catalyst in a high oxidation state and the catalyst is reduced in this first reaction step. In a second reaction step the catalyst is reoxidized separately. DuPont's circulating reactor-regenerator principle thus limits total oxidation of feed and products by the absence of gas phase oxygen in the reaction step of hydrocarbon oxidation [12].

The direct chlorination of methane is carried out as a radical reaction in the gas phase and the highly exothermal reaction produces a mixture of chlorinated methanes (Table 1, entry 6). Higher chlorination is achieved by recycling lower

chlorinated products into the process [13, 14]. If dichloromethane is the desired product, a large excess of methane must be used, as dichloromethane is more rapidly chlorinated than methane. Several process modifications (bubble columns, fluidized bed, tubular reactor, and photochemical initiation) have been developed to overcome the obstacles of high exothermicity, run-away-problems, low product selectivity, and corrosion as a result of formation of hydrochloric acid.

As is apparent from the examples described above, process development of gas-phase reactions involving alkanes is limited by several obstacles:

- corrosion and low stability of reactor materials
- high process temperatures and temperature control
- high pressure
- explosion limits
- limited stability of desired products, decrease in selectivity because of consecutive reactions
- economic necessity of large-scale production
- catalyst deactivation

These obstacles are also crucial for conversion of olefins and aromatics, as will be discussed in Sections 2.3 and 2.4. It is the task of reaction engineering experts to develop reactors and designs for large-scale synthesis while controlling the kinetics of reactions. The kinetics of gas-phase processes are often in the range of milliseconds (HCN synthesis) to seconds (maleic anhydride synthesis). The high reaction temperatures, in particular, require careful selection of reactor materials that are stable and do not act as catalysts or initiators of gas-phase reactions. Processes operated at high pressures make the choice of reactor material even more difficult. Energy supply and, more often, removal of heat from the reactor system is difficult, especially in large scale reactors used for highly exothermic reactions. This has led to a number of solutions, for example fluidized bed reactors, catalytic wall reactors, short-contact-time reactors and quenched reactors. Uncontrolled release of heat in the reactor always favors consecutive reactions reducing the overall selectivity. It can, furthermore, even lead to a run-away and destruction of the reactor.

A problem that must be carefully considered is the occurrence of side- and consecutive reactions. This is especially important for alkane activation, because severe reaction conditions are necessary to activate the C–H bonds. When reactions are fast, as in the HCN and acetylene syntheses, rapid quenching of the reaction products is possible. Another way of affecting selectivity is to limit the partial pressure of reactants, thus also reducing the partial pressure of the desired product. In this way in the maleic anhydride synthesis conversion is limited by diluting the gas and limiting the amount of oxygen available for the reaction.

When employing higher alkanes as a feedstock, process economics are often determined more by selectivity than by conversion per single pass. Most of these reactions are therefore conducted in the liquid phase, which enables easier control of reaction rates and also of side and consecutive reactions by adjustment of the temperature. However, activating alkane C–H bonds always requires reactions

conditions which also favor these unselective reactions. If the rates of production of the desired product and by-products are similar, influencing product selectivity by process design becomes very difficult. As the examples summarized in Table 1 illustrate, few processes are used industrially for C–H transformation of alkanes.

Inserting oxygen into the C–H bond of an alkane initially leads to hydroperoxides. When this reaction is performed with atmospheric oxygen it is also called autooxidation. It usually leads to a multitude of products, because of further spontaneous reactions, so this reaction is of limited synthetic use. An exception is oxidation of isobutane with oxygen, which leads to 70 % yield of *tert*-butyl hydroperoxide at a conversion of 80 % (Table 1, entry 7). Hydrogen bromide is used, among other compounds, as an initiator [15]. *tert*-Butyl hydroperoxide is used as an oxidant in propylene oxide production by the Halcon process. In the formation of phenol by the cumene process cumene is oxidized into the corresponding hydroperoxide in a similar way.

The Bashkirov oxidation (liquid-phase oxidation of *n*-alkanes or cycloalkanes in the presence of boric acid and hydrolysis) yields the corresponding secondary alcohols [16, 17]. The reaction is used industrially for oxidation of C₁₀ to C₁₈ *n*-alkanes, providing raw materials for detergents and for oxidation of cyclododecane to cyclododecanol as an intermediate for the production of Nylon 12 (Table 1, entry 8). The process is not of much commercial importance in the western world, however. Oxidation in the absence of boric acids usually leads to mixtures of alcohols, ketones, and carboxylic acids (Table 1, entry 9).

Of the large number of possible ways of synthesizing alkanesulfonates, only sulfochlorination of alkanes (conversion with sulfur dioxide and chlorine to form alkane sulfonyl chlorides and their saponification with sodium hydroxide; Table 1, entry 10) and sulfoxidation (reaction with sulfur dioxide and oxygen and neutralization of the sulfonic acids; Table 1, entry 11) are of industrial importance [18].

The catalytic oxidation of cyclohexane is performed in the liquid phase with air as reactant and in the presence of a catalyst. The resulting product is a mixture of alcohol and ketone (Table 1, entry 12) [19]. To limit formation of side-products (adipic, glutaric, and succinic acids) conversion is limited to 10–12 %. In a process developed by Toray a gas mixture containing HCl and nitrosyl chloride is reacted with cyclohexane, with initiation by light, forming the oxime directly (Table 1, entry 12). The corrosiveness of the nitrosyl chloride causes massive problems, however [20]. The nitration of alkanes (Table 1, entry 13) became important in a liquid-phase reaction producing nitrocyclohexane which was further catalytically hydrated forming the oxime.

Another example of the use of natural gas is the reaction of methane with sulfur over silica gel as catalyst at temperatures around 650 °C forming carbon disulfide (Table 1, entry 14). CS₂ is still used for production of CCl₄.

Alkane activation can also be achieved under very mild reaction conditions. This is demonstrated by the use of microorganisms for transformation of *n*-alkanes into proteins by oxidation (Table 1, entry 15).

The activation of alkanes is becoming increasingly relevant because of the expected shortage of crude oil. With the demand for energy and chemicals rising,

there is, especially in Asia, a tendency to go back to the use of coal as a raw material. Furthermore, biomass as a renewable resource starts to become interesting for ensuring future resources of different carbon fractions. New processes which are close to commercialization are summarized in Table 2. The direct use of natural gas is of particular interest. Direct conversion to methanol (Table 2, entry 16) would facilitate transport of natural resources from the respective deposits to large-scale production sites. Direct synthesis would also make the step of synthesis-gas production (Table 1, entry 2) no longer necessary in routes leading to higher hydrocarbons, for example the methanol-to-olefins (MTO) process [21]. Direct synthesis of formaldehyde, as one of the most reactive intermediates in industrial chemistry is also an aim of process development. Another way to produce higher hydrocarbons from natural gas is the transformation of C–H bonds in methane into C–C bonds by (oxidative) coupling of methane (Table 2, entry 17). Extensive research work has been conducted on this process [22]. It seems, however, there is an internal barrier that limits yields to values below 25 %, which would make the coupling of methane economically feasible.

Table 2. New processes for alkanes under development and close to commercialization.

	Starting material	Reactant/condition	Product
16	C ₁	O ₂	CH ₃ OH (CH ₂ O) [21]
17	C ₁	O ₂	C ₂₊ [22]
18	C _x	Metal catalyst	Carbon nanotubes/carbon nanofibers/ buckyballs [27–29]
19	C ₃	O ₂	Acrolein, acrylic acid [23, 24]
20	C ₃	O ₂ /NH ₃	Acrylonitrile [25, 26]
21	C ₃ /C ₄	Catalyst	BTX aromatics [10]

Since the early 1990s several methods have been used to transform the C–H bonds of methane and higher hydrocarbons directly into highly ordered C–C bonds in a nano-scaled product; such work has attracted much attention in recent years in attempts to manufacture carbon nanotubes, nanofibers, and buckyballs [27–29]. The production of nanoscaled carbon material is already well established – annual production of carbon black is approx. 8×10^6 metric tons per year. In contrast with carbon black, nanotubes and fibers have highly ordered structures. These are of special interest because of their unique properties, for example high mechanical strength, excellent electrical and thermal conductivity, and very high ratio of length (up to tens of microns) to diameter (usually 3–150 nm). Furthermore, the possibility of functionalizing the carbon atoms on the outer layer of nanotubes, thus building complex structures, makes many new applications pos-

sible. Processes are based on the decomposition of hydrocarbons, e.g. CH_4 , at high temperatures (600–1200 °C), on metal catalysts based on, e.g., iron or nickel [27–29]. Process economics and yields must still be improved to make carbon nanotubes in a way that can compete with established products in the mass markets.

Further examples of attempts to replace olefins by alkanes as a starting materials, as in the maleic anhydride process, are the development of processes for selective oxidation and ammoxidation. Examples are processes for acrolein, acrylic acid (Table 2, entry 19) and acrylonitrile (Table 2, entry 20) using propane as a feedstock [30]. As discussed at the beginning of this section, the difficulty of activating short alkanes causes selectivity problems in these oxidation reactions. Intermediates formed in the, usually, consecutive reaction mechanisms are less stable than propane against further oxidation, and total oxidation and cracking occur as side reactions limiting the selectivity compared with the first vanadia-based catalysts [31]. The development of a complex mixed-oxide catalyst brought the activity and selectivity of the catalyst into a range in which the process may become economically feasible and it has been announced that pilot and demonstration plants are to be brought into operation, partly working with a mixed feed of olefin and alkane [32].

Dehydrocyclodimerization of liquefied petrol gas (propane and butane) can be performed to yield BTX-aromatics (Table 2, entry 21). Modified ZSM-5 based catalysts are used, for example in the UOP cyclar process [33], and the process will become attractive for extraction of aromatics from natural gas fields containing further C_3 – C_4 fractions.

2.3

C–H Transformation at Olefins

In many olefinic reactions activation of the $\text{C}=\text{C}$ double bond occurs, although in many reactions at least one C–H bond is transformed. Established processes are summarized in Table 3. Examples of liquid-phase reactions are the synthesis of ethers, especially methyl *tert*-butyl ether by reacting olefins (*isobutene*) and alcohol (methanol) in the liquid phase at slightly elevated temperature and pressure (Table 3, entry 22). Different processes developed differ only slightly in feed composition and design, which is optimized for heat removal [2].

In the direct oxidation of ethylene to yield acetaldehyde (Table 3, entry 23), aqueous solutions of a catalyst and slightly elevated temperatures (100–150 °C) are used [34]. For process development the corrosion caused by the CuCl_2 and PdCl_2 solutions used as catalysts was crucial.

In the industrial production of acetic acid the main production routes are based on the carbonylation of methanol, a process which was first developed in the 1940s. Although the process remains cheap, the availability and pricing of raw materials have forced the development of new processes based on the direct oxidation of ethylene to form acetic acid (Table 3, entry 24). Complex multimetal oxide

catalysts are suitable [35, 36], and routes employing ethane have also been investigated [37]. Although C_2 is an inexpensive raw material and high selectivity has been achieved [23], it is unlikely that direct oxidation, based on ethane, will compete with carbonylation of methanol in the near future. The oxygen concentration must be limited for safety reasons and, therefore, conversion per single pass is limited.

Table 3. C–H transformation processes of olefins.

	Starting material	Reactant/condition	Product
22	C_x	ROH	MTBE, ether [2]
23	C_2	$O_2/PdCl_2$	Acetaldehyde [34]
24	C_2	O_2	Acetic acid [35–37]
25	C_3	O_2	Acrolein, acrylic acid [38–40]
26	C_3	O_2/NH_3	Acrylonitrile [42, 43]
27	C_4	O_2	Maleic anhydride
28	$C=CH_2$	Cl_2 , dehydrochlorination	$C=CHCl$, e.g. chloroprene [44, 45]

The direct heterogeneously catalyzed oxidation of propylene yielding acrolein was commercialized in the 1960s (Table 3, entry 25). Complex metal oxide catalysts [38–40] were developed, and oxidation with air is performed in tubular reactors. Propylene is diluted with air and steam. The multitubular reactors are cooled by molten salt baths to remove the heat of reaction [41]. The ammoxidation of propylene is also a well established process (Table 3, entry 26). In the so called Sohio process high conversion and selectivity are achieved by controlling the temperature in fluidized bed reactors with internal cooling [42, 43]. In his process higher conversions are possible because of the greater stability of acrylonitrile compared with acrolein against total oxidation. Ammonia and propylene are fed separately into the reactor to avoid explosive mixtures. Other processes known employ cooled fixed bed multitubular reactors.

As described above, butylene is employed as part of the feedstock in maleic anhydride synthesis (Table 3, entry 27). Process conditions are similar but, because of the pricing of feedstocks, butane oxidation is mainly employed.

Chloroprene is of high industrial importance for manufacture of synthetic rubbers. For a long time the synthesis was based on acetylene. More recent processes are based on butadiene as a feedstock, which is substantially cheaper [29]. The initial step is a gas-phase free-radical chlorination at 250 °C and temperature control is ensured by use of excess butadiene (molar ratio of Cl_2 to butadiene: 1:5 to 1:50) [44]. To limit side reactions, short contact time reactors operating at higher temperatures and residence times below one second are also known [45]. Good mix-

ing of reactants is crucial, to prevent formation of soot. The excess butadiene is recycled into the chlorination reactor. The chlorination yields a mixture of the 1,2- and 1,4-adducts. The latter can be isomerized to the 1,2-adduct by use of catalytic amounts of copper or iron salts. In a second step dehydrochlorination is performed in a dilute alkaline solution. Addition of phase-transfer catalysts increases the reaction rate.

2.4

Basic Chemicals from Aromatic Hydrocarbons

The transformation of C–H bonds in aromatic hydrocarbons has numerous applications, yielding a broad variety of chemicals. The variety of reactions does not enable description of process characteristics and chemistry in detail here. As already stated in the introduction, more details are readily available in the general literature [1–3].

Table 4. Basic functionalization of aromatic hydrocarbons.

	Starting material	Reactant	Product
29	Benzene	Olefin/Catalysts	Ethyl-, isopropylbenzene
30	Benzene	Propene/O ₂	Phenol/acetone
31	Benzene	Cl ₂ , catalyst	Chlorinated benzenes
32	Toluene	Cl ₂	Chlorinated toluenes
33	<i>p</i> -Xylene	O ₂ /Co/Mn	Terephthalic acid
34	<i>o</i> -Xylene/naphthalene	O ₂ /VPO	Phthalic acid
35	Benzene	HNO ₃ /H ₂ SO ₄ , H ₂	Nitrobenzene, aniline
36	Toluene	HNO ₃ , H ₂ , COCl ₂	Nitrotoluene, TDI
37	Toluene, xylene	Cl ₂	Side-chain chlorinated products
38	Benzene	SO ₃ /H ₂ SO ₄	Benzenesulfonic acid, tensides
39	Phenol	CO ₂	Salicylic acid
40	Toluene	O ₂	Benzoic acid
41	Nitrotoluene	O ₂	Nitrobenzoic acid

The alkylation of benzene is the most important reaction in the further use of this compound (Table 4, entry 29) [1]. The reaction is performed in the liquid phase with Friedel–Crafts catalysts or in the gas phase with acid catalysts such as H₃PO₄, aluminum silicates, or BF₃. More than 50 % of benzene consumption

goes into the production of ethylbenzene, which is further converted to styrene by direct catalytic dehydrogenation. It is important to note that in the dehydrogenation process, carried out at high temperatures, once again the partial pressure of ethylbenzene is reduced by co-feeding water vapor to limit side reactions. The alkylation of benzene with propene (Table 4, entry 30) yields cumene, which is almost exclusively used in the Hock process for the manufacture of phenol and acetone, a process commercialized in the 1950s. Higher alkylbenzenes are starting materials for the corresponding sulfonates, which are converted further into surfactants and detergents.

Chlorination of benzene was industrially established by liquid phase reaction with FeCl_3 catalysts. In the oxychlorination process (Raschig–Hooker process) HCl/Air mixtures are used at a reaction temperature of 240°C and atmospheric pressure. Fixed bed catalysts ($\text{CuCl}_2/\text{FeCl}_3/\text{Al}_2\text{O}_3$) are used and conversion must be limited to below 20 % to suppress formation of higher chlorinated products. In the Raschig–Hooker process hydrolysis occurs catalytically yielding HCl , avoiding the production of NaCl , and limiting the amount of HCl needed. Disadvantages of the gas-phase process are the high investment costs for corrosion-resistant plants, large energy costs, and the need for frequent regeneration of the hydrolysis catalyst, because of coke formation. Chlorination of toluene (Table 4, entry 32) is important in the production of chlorotoluene, which is a basis for further production of cresols.

The oxidation of *p*-xylene to terephthalic acid (Table 4, entry 33) would only result in the formation of *p*-toluic acid. To convert the second group in high yield and selectivity, the oxidation must be influenced in one of three ways:

- conversion of the carboxyl group into an ester followed by oxidation of the second methyl group;
- addition of a co-catalyst (often a bromine compound); or
- co-oxidation in a process in which an auxiliary substance capable of supplying peroxides (e.g. acetaldehyde, paraldehyde, methyl ethyl ketone) is simultaneously oxidized

These dimethyl terephthalate and terephthalic acid processes illustrate that it can be necessary to modify the reaction chemistry and mild (liquid phase) conditions to obtain the product in the desired yield and purity.

In the oxidation of naphthalene or *o*-xylene forming phthalic anhydride simple oxidation is sufficient (Table 4, entry 34). As in all heterogeneously catalyzed oxidation reactions with high exothermicity, oxidation of naphthalene or *o*-xylene over vanadium oxide catalysts is carried out in multitubular or fluidized bed reactors, enabling removal of the heat of reaction. It is also necessary to cool the reaction mixture from the reaction temperature ($360\text{--}420^\circ\text{C}$) to temperatures below the dew point of phthalic anhydride to avoid consecutive reactions. This task is difficult in large-scale operation and led, e.g., to the development of a two-stage fluidized-bed process. In the fluidized bed process the reaction is operated within flammability limits, the catalyst particles acting as an effective dispersal medium preventing an explosion. *o*-Xylene oxidation is also performed in the liquid phase

using Co, Mn, or Mo-based catalysts. This technique is of minor importance for larger scale production (a phthalic anhydride world scale plant operates at 50 000 metric tons/year in one reactor).

Nitration of benzene (Table 4, entry 35) is usually conducted using a mixture of nitric acid and sulfuric acid (nitrating acid). Sulfuric acid promotes the formation of the nitronium ion, prevents dissociation of nitric acid and enhances solubility between phases. The process is still performed batch-wise at temperatures of 50–60 °C. Vigorous stirring of the two-phase reaction mixture is necessary for both mass and heat exchange and residence times are in the range of several hours. Continuous nitration plants consist of cascades of vessels. The purified nitrobenzene is reacted with hydrogen using a heterogeneous catalyst to form aniline. Fixed beds (Bayer) and fluidized beds (BASF) are used as reactors in this exothermic hydrogenation. In an analogous process toluene is nitrated to dinitrotoluene (Table 4, entry 36). Hydrogenation is carried out catalytically with copper, palladium, or nickel catalysts in solvents like methanol. In contrast with aniline, gas-phase hydrogenation is not possible.

Side-chain chlorinated alkyl aromatics based on toluene and xylene play an important role as chemical intermediates. They are used in the manufacture of a variety of chemical products including plastics, pharmaceuticals, flavors, pesticides, catalysts, and more. Monochlorination of the sidechain (Table 4, entry 37) is rather difficult.

The sulfoxidation of benzene (Table 4, entry 38) yields benzenesulfonic acids and the respective derivatives. The electrophilic aromatic substitution reaction gives high yields and aqueous sulfuric acid or oleum is used for the sulfonation reaction, which is performed in cascades of reactor vessels.

The carboxylation of phenols is a well established process for synthesis of salicylic acid according to the Kolbe–Schmitt method (Table 4, entry 39). The exothermic reaction is carried out at slightly elevated temperatures around 150 °C and pressures of approximately 5 bar. Batch processes are still mainly used. The main task is to exclude water from the reaction mixture, because this would release the alkali metal hydroxide from the phenoxide salt.

The liquid-phase oxidation of toluene with molecular oxygen is another example of a well established process (Table 4, entry 40). A cobalt catalyst is used in the process and the reaction proceeds via a free-radical chain mechanism. Heat of reaction is removed by external circulation of the reactor content and both bubble columns or stirred tanks are employed. It is important to note that air distribution is critical to prevent the danger of a runaway. Another example of direct oxidation is the commercial production of nitrobenzoic acid by oxidation of 4-nitrotoluene with oxygen (Table 4, entry 41).

Apart from development of new catalysts with enhanced activity, few processes with innovative chemistry are currently developed for C–H transformation in aromatics. Though new processes using cheaper raw materials or reducing the number of reaction steps may seem attractive at first glance, efforts for process development including research, scale-up, pilot plant, and timeline must be considered. Especially for large scale-synthesis of bulk chemicals process economics

Table 5. New processes for C–H transformation in aromatic hydrocarbons.

	Starting material	Reactant/condition	Product
44	Benzene	N ₂ O	Phenol [46, 47]
45	Cresols	O ₂	Hydroxybenzaldehydes [49]

must be taken into account. Potential new processes therefore have to show a significant potential in reduction of production costs in the early stage of development to go into further scale-up.

An interesting new process is the conversion of benzene to phenol with N₂O developed by the Boreskov Institute for Catalysis and Solutia [46, 47]. Important for the process is the in-situ generation of active oxygen on the catalyst – so called α -oxygen – minimizing the content of free oxygen in the gas phase. This elegant approach generates an active oxygen species which is inserted into the C–H bond. Thus highly selective oxygen is generated on the catalyst. The amount of free oxygen in the gas phase is on a very low level and attack of the aromatic ring and total oxidation is minimized. The catalyst must be regenerated periodically, because of deactivation after coke-formation. Though the yield and selectivity of the process are high and only one step is required for conversion of benzene, it is not yet commercialized. One reason is the need to construct a world-scale size plant to be economically competitive. Furthermore N₂O has to be generated in sufficient amounts for the reaction, e.g. by oxidation of ammonia. The ability to insert this oxygen was also demonstrated for C–H bonds in methane, forming methanol [48], but the overall space–time yield was too low for large-scale synthesis.

Another example of minimizing the reaction steps necessary for synthesis is the direct conversion of cresols into hydroxybenzaldehydes, replacing the Reimer–Tiemann reaction in which phenol is reacted with chloroform in the presence of KOH. Hydroxybenzaldehydes are used in pharmaceuticals, perfumes, and colors. In the direct oxidation cresols are reacted with oxygen in the presence of Cu/Co/C catalysts forming the salicylaldehyde [49].

2.5

Fine Chemicals

In the synthesis of fine chemicals the same types of reaction often employed in the formation of basic chemicals (see Sections 2.5.1 and 2.5.2) are used. Furthermore, the same or similar starting materials may be used. There are usually two routes to obtain fine chemicals from C–H transformation that differ with regard to the basic chemicals. One way is to start with a simple substrate e.g. methane and perform a complex functionalization in one step. Most research in the field of fine chemistry is focused in this field. Another way is to start with a more complex starting material and carry out a C–H transformation step with very high selectiv-

ity to reduce the amount of wasted starting material and increase the economic value of the synthesis.

Furthermore, in the synthesis of fine chemicals typical process technology considerations, for example space-time-yield, are less important than for bulk chemicals. Because of the relatively small production outputs batch reactors are the most common apparatus in which to perform the synthesis. New chances in the field of fine chemistry may be offered by micro-reaction technology. Microstructured systems can be used to improve heat transfer which may be critical for highly exothermic reactions and, furthermore, they may be also useful in reactions where fast mixing of components is recommended.

The C–H transformation in the synthesis of fine chemicals can be separated in reactions employing catalysis by organometallic compounds and metal-free synthesis. Organometallic catalyzed functionalization is usually performed in liquid or gas/liquid reactions whereas the metal-free synthesis of fine chemicals often occurs as a gas-phase reaction.

2.5.1

Fine Chemicals by Organometallic Catalysis

Functionalization of alkanes to produce fine chemicals uses many different reaction types that cannot be listed completely within this introduction. An overview of typical reactions, for example halogenation, dehydration, borylation, oxidation, and hydroxyalkylation, is given in Table 6.

Table 6. Organometallic catalyzed functionalization of alkanes.

Starting material	Reactant/conditions	Product
46 Alkane	$\text{Cl}_2/[\text{Pt}(\text{Cl})_4]^{2-}$	Chloroalkanes [50]
47 Cyclooctane/vinyl- <i>tert</i> -butane	$\text{ReH}_7(\text{PR}_3)_2$	Cyclooctene/ethyl- <i>tert</i> -butane [51]
48 Methylcyclohexane	$\text{IrH}_2(\text{O}_2\text{CCF}_3)(\text{PR}_3)_2$, UV	Methylenecyclohexane [52]
49 Alkane	$\text{R}_2\text{B-BR}'_2$, $\text{CpRh}(\text{C}_2\text{H}_4)_2$, UV	Boroalkane [53]
50 Cyclohexane	CH_3OH , Hg, UV	Hydroxymethylenecyclohexane [54]

The platinum-catalyzed reaction of alkanes with chlorine leads to alkyl chlorides and alcohols (Table 6, entry 46) with modest rates and conversions [50]. Cyclooctane can be easily dehydrogenated (Table 6, entry 47) in the presence of a stabilized vinylalkane by use of the neutral rhenium compound $\text{ReH}_7(\text{PR}_3)_2$ [51]. By employing an iridium-based catalyst, the photochemical dehydrogenation of methylcyclohexane to methylenecyclohexane is performed at room temperature

(Table 6, entry 48) whereas alkene isomerization is very slow [52]. Photochemistry is also used in the rhodium-catalyzed alkylborylation of alkanes in which boroalkanes (Table 4, entry 49) are obtained [53]. An example of a gas-phase reaction is the photochemical mercury-catalyzed hydroxymethylation of cyclohexane to hydroxymethylenecyclohexane (Table 6, entry 50). This reaction is an example of the abstraction of a hydrogen atom from an alkane by an excited metal atom [54].

The activation and transformation of C–H bonds in alkanes by homogeneous transition metal catalysts should to be a topic of further research. No processes are close to commercialization on a technical scale. So far the organometallic approach by Shilov is one of the most promising ways of producing a practical system [55].

2.5.2

Metal-free Synthesis of Fine Chemicals

An overview of some metal-free reactions, for example oxidation, amination, and halogenation, is given in Table 7.

Table 7. Metal free reactions.

	Starting material	Reactants/conditions	Product
51	2,3-Dimethylbutane	O ₂ , UV	Acetone, 2,3-dimethylbutanehydroperoxide [56]
52	Methane	O ₂ /NO ₂	Formaldehyde, CO, nitromethane [57]
53	Cyclohexane	O ₂ /NO ₂	Cyclohexanal, nitrocyclohexane [58]
54	Adamantane	NHPI/O ₂	Adamantanol [59]
55	Adamantane	H ₂ O ₂ /O ₂	Adamantanol/adamantanal [60]
56	Cyclohexane	O ₂ /Zeolite NaY, UV	Cyclohexanehydroperoxide/cyclohexanal [61]
57	Cyclohexane	NHPI/NO ₂ /O ₂	Nitrocyclohexanes [62]
58	Ethane	NH ₃ /Hg, UV	Imines [63]
59	Cyclohexane	HCl ₃ /NaOH/phase transfer catalyst	Iodocyclohexane [64]
60	2-Chloroacetic ester	HCOOH/F ₂ /N ₂	2,2-Chlorofluoroacetic ester [65]
61	Methane	NH ₃ /O ₂ /N ₂	HCN [66]

The gas phase oxidation of 2,3-dimethylbutane (Table 7, entry 51) leads to number of products even under mild conditions [56]. The selectivity of alkane oxidations, e.g. methane oxidation (Table 7, entry 52) increases substantially in the pres-

ence of nitrogen oxides but are still below 10 % [57]. For many alkanes, e.g. cyclohexane, the gas-phase oxidation (Table 7, entry 53) is unselective because of fragmentation reactions [58]. The selectivity of alkane oxidations can be improved by using oxygen and NHPI (*N*-hydroxyphthalimide; Table 7, entry 54), often in the presence of a cobalt catalyst under mild conditions [67]. By using NHPI, which forms PINO (phthalimide-*N*-oxyl) radicals in situ, adamantane can be oxidized to adamantanol with 52 % yield [59]. Classical reagents, for example $\text{H}_2\text{O}_2/\text{O}_2$, lead to a mixture of adamantanol and adamantanal (Table 7, entry 55) [60]. Another approach to selective photochemical oxidation of cyclic alkanes is the oxidation of cyclohexane (Table 7, entry 56) using zeolite NaY and leading to conversion of 40 % [61]. Furthermore, NHPI may be used in the nitration of alkanes. Functionalizations with the NHPI/ NO_2/O_2 system are very effective in catalytic selective nitration of alkanes (Table 7, entry 57) under mild conditions [62]. Direct photochemical-induced imination of short-chain alkanes in the gas phase has been developed using alkane/ammonia mixtures in the presence of mercury vapor (Table 7, entry 58), leading to a mixture of methylenimine and higher imines [63]. Selective halogenation of alkanes may be achieved by using more complex halogen compounds (Table 7, entry 59). The reaction of cyclohexane with iodoform (CHI_3) in the presence of a base and a phase-transfer catalyst leads to the formation of iodocyclohexane [64]. Fluorination (Table 7, entry 60) is usually the most difficult halogenation reaction, because high exothermicity often makes the reaction uncontrollable in conventional reactors [68]. The reaction of ethyl 2-chloroacetate in a microreactor resulted in conversion of 59 % and a yield of 74 %, these values are significantly higher than for conventional reactors [65].

This example shows another trend in the field of fine chemicals – the use of micro technology, especially for reactions that must be performed under extreme conditions because of thermodynamic limitations. Another example of reactions under extreme conditions carried out using micro reaction technology is the Andrussov synthesis. This is the reaction of methane in the presence of ammonia and oxygen/nitrogen to form HCN that is performed at temperatures above 1000 °C (see also Section 2.2) [66]. In addition to the examples mentioned, micro reaction technology can be used to overcome obstacles such as exothermicity and temperature control in general, narrow explosion limits, highly reactive reactants, and influence of residence time distribution. Scale-up is easy in parallel systems, and modular designs can be used. These advantages will lead to broad application of this emerging technology in the synthesis of chemicals.

References

- 1 K. Weissmehl, H.-J. Arpe, *Industrial Organic Chemistry*, 4th edn, Wiley–VCH, Weinheim, 1978–2003
- 2 *Ullmann's Encyclopedia of Industrial Chemistry*, 6th edn, Wiley, New York, 2003
- 3 R.E. Kirk, D.F. Othmer, *Encyclopedia of Chemical Technology*, 4th edn, Wiley, New York, 1998
- 4 Montecatini, GB 1000480, 1962, *Acetylene Production*
- 5 BASF, DE 879989, 1953, H. Klein, H. Sachsse, W. Hofditz, F. Haubach, *Verfahren zur Gewinnung von Acetylen*
- 6 BASF, DRP 296 866, 1912
- 7 L. Andrussov, *Angew. Chem.* 1935, 48(37), 593–604
- 8 Degussa, DE 959364, F. Endter, 1954, *Vorrichtung zur Durchführung einer endothermen Gasphasenreaktion*
- 9 Shawinigan Chemicals Ltd, US 3097921, D.J. Kennedy and N.B. Shine, 1963, *Production of Hydrogen Cyanide*
- 10 M.S. Scurrrell, *Appl. Catal.* 1987, 32, 1
- 11 Monsanto Co., J.T. Wrobelski, US 4456764, 1982, *Process for the production of maleic anhydride*
- 12 Du Pont, DE 197 42 935, 1998, R.M. Contractor, H.S. Horowitz, J.D. Sullivan, *Verbessertes Verfahren zur Kalzinierung/Aktivierung eines V-P-O-Katalysators*
- 13 Hoechst, GB 1 400 855, 1975, *Process for the manufacture of chloromethanes by thermal chlorination*
- 14 Chemische Werke Hüls, A. Schmidt, J. Tiesler, DE 1 188 571, 1965, *Verfahren zur Chlorierung von Kohlenwasserstoffen bzw. Chlorkohlenwasserstoffen*
- 15 Shell, US 2 403 772, 1946; Shell, US 2 845 461, 1958
- 16 I.M. Towbin, D.M. Boljanowskii, *Maslo. Zhir. Promst.* 1966, 32, 29
- 17 F. Püschel, *Tenside Deterg.* 1971, 11, 147
- 18 Aventis, DE 19905613, A. Hagemeyer und K. Kühlein, 2000, *Photoinitiierung der Sulfochlorierung oder Sulfoxidation von Alkanen*, and references cited therein
- 19 Du Pont, US 3530185, 1970, K. Pugi, *Oxidation Process*
- 20 Toyo Rayon, DE 1150975, 1960, A. Yoshikazo Ito, *Verfahren zur Herstellung von Nitroverbindungen oder Oximen*
- 21 Y. Wang, K. Ostsuka, *J. Chem. Soc. Chem. Commun.* 1994, 2209
- 22 M. Baerns, G. Grubert, E.V. Kondratenko, D. Linke, U. Rodemerck, DGMK Tagungsbericht 2002–4, 61–78, *Alkanes as substitutes for alkenes in the manufacture of petrochemicals – a continuing challenge of the present and future*
- 23 O.V. Buyevskaya, M. Baerns, *Catalysis*, 2002, 16, 155
- 24 R.K. Grasselli, *Catal. Today*, 1999, 49, 141
- 25 R.K. Grasselli, G. Centi, F. Trifiro, *Appl. Catal.*, 1990, 57, 149
- 26 Mitsubishi, EP 0 318 295, 1989, A. Kayo, T. Umezawa, K. Kiyono, I. Sawaki, *Process for the production of nitriles*
- 27 K.P. DeJong, J.W. Geus, *Catal. Rev.–Sci. Eng.*, 2000, 42(4), 481
- 28 Showa Denko, JP 62078125, 1987, *Carbon fibre mfr. in vapour phase – by thermally decomposing organic transition metal cpd., feeding into zone at 1000–1300 deg C and adding another organic cpd. Gas*
- 29 Hyperion Catalysis International, US 4663230, H.G. Tennent, 1986, *Carbon Fibrils, Method for Producing Same, and Compositions Containing Same*
- 30 G. Centi, R.K. Grasselli, E. Patane und F. Trifiro, *Stud. Surf. Sci. Catal.*, 55, Ed. G. Centi and F. Trifiro, 1990, Elsevier Science Publishers, Amsterdam, *Synthesis of Acrylonitrile from Propane over V-Sb-based Mixed Oxides*
- 31 Standard Oil Company, US Patent US 4,746,641, 1988, A.T. Guttman, R.K. Grasselli, J.F. Brazdil, *Ammonoxidation of paraffins and catalyst therefor*
- 32 Mitsubishi Chemical Corporation, EP 529 853 B1, 1989, A. Kayo, T. Umezawa, K. Kiyono, I. Sawaki, *Process for producing nitriles*
- 33 BP Chemicals Limited, US 4,761,511, M.T. Barlow, 1988, *Crystalline galloaluminosilicates, steam-modified crystalline gal-*

- loaluminosilicates, their preparation and their use as catalysts and catalyst supports
- 34 Consortium für Elektrochemie, DE 1 049 845, W. Hafner, J. Smidt, R. Jira, R. Rüttinger, J. Sedlmeier, 1957, *Verfahren zur Herstellung von Carbonylverbindungen*
 - 35 J.L. Seone, P. Boutry, R. Montarnal, *J. Catal.* **1980**, 63, 182–190
 - 36 Showa Denko, DE 694 12 326 T2, 1999, T. Suzuki, Y. Toshiro, K. Abe, K. Sano *Verfahren zur Herstellung von Essigsäure*
 - 37 Union Carbide Corporation, EP 2161264 A1, 1986 R.M. Manyik, J.L. Brockwell, J.E. Kendall, *Process for the oxydehydrogenation of ethane*
 - 38 Nippon Kayaku, US 3454630, 1969, G. Yamaguchi, S. Takenaka, *Process for the oxidation of olefins to aldehydes and acids*
 - 39 Sumitomo Chemical Co., EP 0630879, 1994, Y. Nagaoka, Y. Nomura, K. Nagai, *Process for the production of an unsaturated carboxylic acid*
 - 40 Mitsubishi Petrochemical Co., EP 239071, 1992, K. Sarumaru, E. Yamamoto, T. Saito, *Production of composite oxidation catalyst*
 - 41 W.M. Weigert, *Chem. Eng.*, **1973**, 80, 15, 68
 - 42 Allied, US 2481826, 1947, J.N. Cosby
 - 43 Standard Oil of Ohio, US 2904580, 1957 J.D. Idol, Jr
 - 44 Du Pont, DE-OS 2 046 007, 1970 O.K. Wayne, J.L. Hatten, *Chlorierung von Butadien*
 - 45 Distillers Co., DE 1 090 652, 1957, C.W. Capp, H.P. Croker, F.J. Bellinger, *Verfahren zur Herstellung von Dichlorbutenen*
 - 46 Boreskov Institute of Catalysis, WO 95/27650 Panov, G.I., Karithonov, A.S., Shelevea, G.A., 1995, *Method for producing phenol and its derivatives*
 - 47 Solutia Inc., 6,156,938, Sobolev, V.I., Rodkin, M.A., Urlarte, A.K., Panov, G.I., 2000, *Process for making phenol or its derivatives*
 - 48 V.I. Sobolev, K.A. Dubkov, O.V. Panna, G.I. Panov, *Catalysis Today* (1995), 24, 251–252, *Selective oxidation of methane to methanol on a FeZSM-5 surface*
 - 49 Wang F, Xu J, Liao S.J., *Chem. Commun. (Camb)*. **2002** Mar 21;(6):626–7, *One-step heterogeneously catalytic oxidation of o-cresol by oxygen to salicylaldehyde*
 - 50 A.E. Shilov, G.B. Shul'pin, *Chem. Rev.*, **1997**, 2879
 - 51 D. Baudry, M. Ephritikine, H. Felkin, J. Zakrewski, *J. Chem. Soc., Chem. Commun.*, **1982**, 1235
 - 52 M.J. Burk, R.H. Crabtree, *J. Am. Chem. Soc.* **1987**, 109, 8025
 - 53 H. Chen, J.F. Hartwig, *Angew. Chem., Int. Ed.* **1999**, 38, 3391
 - 54 R.H. Crabtree, *Pure Appl. Chem.* **1995**, 67, 39
 - 55 R.H. Crabtree, *J. Chem. Soc., Dalton Trans.* **2001**, 2437
 - 56 G. Heimann, P. Warneck, *J. Phys. Chem.* **1992**, 96, 8403
 - 57 K. Tabata, Y. Teng, Y. Yamaguchi, H. Sakurai, E. Suzuki, *J. Phys. Chem.* **2000**, 104, 2648
 - 58 S.M. Aschmann, A.A. Chew, J. Arey, R. Atkinson, *J. Phys. Chem.* **1997**, 101, 8042
 - 59 Y. Ishii, S. Kato, T. Iwahama, S. Sakaguchi, *Tetrahedron Lett.* **1996**, 37, 4993
 - 60 G.B. Shul'pin, Y.N. Kozlov, G.V. Nizova, G. Süß-Fink, S. Stanislas, A. Kitaygorodskij, A.S. Kulikova, *J. Chem. Soc. Perkin, Trans. 2*, **2001**, 1351
 - 61 H. Sun, F. Blatter, H. Frei, *J. Am. Chem. Soc.* **1996**, 118, 6873
 - 62 S. Sakaguchi, Y. Nishiawaki, T. Kitamura, Y. Ishii, *Angew. Chem. Int. Ed. Engl.* **2001**, 40, 222
 - 63 P. Krajník, D. Michos, R.H. Crabtree, *New J. Chem.* **1993**, 17, 805
 - 64 P.R. Schreiner, O. Lauenstein, E.D. Butova, A.A. Fokin, *Angew. Chem. Int. Ed. Engl.* **1999**, 38, 2786
 - 65 R.D. Chambers, D. Holling, R.C.H. Spink, G. Sandford, *Lab Chip*, **2001**, 1, 132
 - 66 V. Hessel, W. Ehrfeld, K. Golbig, C. Hofmann, S. Jungwirth, H. Löwe, T. Richter, M. Storz, A. Wolf, O. Wörz, J. Breysee, in, *Proc. 3rd Int. Conf. Microreaction Technology*, **1999**, Springer, Berlin, 151
 - 67 Y. Ishii, S. Sakaguchi, T. Iwahama, *Adv. Synth. Catal.* **2001**, 343, 393
 - 68 K. Jähnisch, M. Baerns, V. Hessel, *Angew. Chem. Int. Ed.* **2004**, 43, 406

II

C–H Transformation at sp -Hybridized Carbon Atoms

1

C–H Transformation at Terminal Alkynes

1.1

Recent Developments in Enantioselective Addition of Terminal Alkynes to Aldehydes

Tobias Ritter and Erick M. Carreira

1.1.1

Introduction

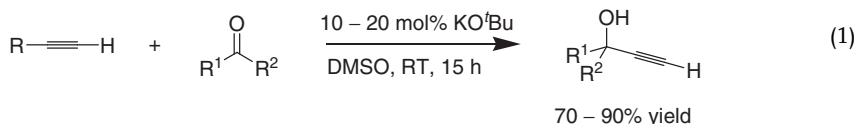
As hydrocarbons, terminal acetylenes enjoy a rich reaction chemistry [1]. This is in no small part because of a unique feature of terminal acetylenes that differentiates them from other hydrocarbons – the acidity of the terminal proton ($pK_a = 25$). It is suggested that the lability of the terminal C–H towards deprotonation results in its being bound to an sp-hybridized carbon [2]. This characteristic has been recognized for some time and has led to a diversity of methods for generation of metal acetylides which can participate in coupling reactions.

Alkynylides typically employed in C=O addition reactions are commonly prepared by acetylene deprotonation with strong bases (e.g. BuLi, RMgBr, LDA) [3]. Because aldehydes can undergo nucleophilic additions or are themselves subject to deprotonation under such conditions, generation of metal acetylides is conducted as a separate step before introduction of the electrophilic aldehyde coupling partner. The ability of terminal acetylenes to undergo metalation in the presence of Ag(I) or Cu(I) salts has been recognized for some time [4] and forms the basis of useful processes, for example the Sonogashira reaction. Acetylides derived from Ag(I) and Cu(I), however, do not readily participate in C=O addition reactions. Recent studies have expanded the conditions that can be used to metalate acetylenes to include other metals, in particular Zn(II). This has enabled the development of novel methods for the synthesis of propargylic alcohols. This chapter will cover the latest developments in acetylene activation and deprotonation to alkynylides which have been used in asymmetric aldehyde addition reactions.

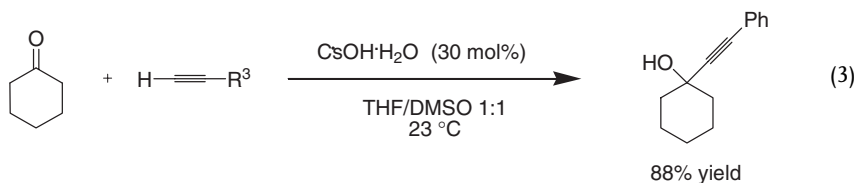
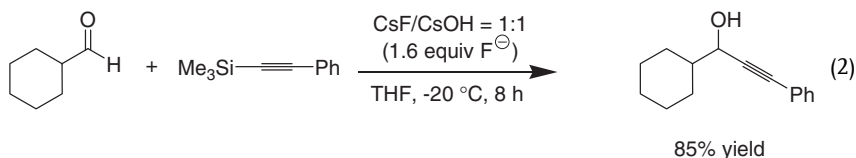
1.1.2

Background

In 1900 Favorski reported the KOH-mediated addition of acetylene to aldehydes and ketones [5]. Acetylene and KOH have been observed to form a 1:1 complex in liquid ammonia to give a solid. The infra-red spectrum of this solid (in Nujol or KBr disks) gave no signals for the C–C and C–H resonances. The complex was also shown to evolve acetylene when heated at 110 °C for 4 h. Several observations were made in the course of these studies that reveal some intriguing nuances of the process. For example, use of an alkali metal acetylide generated by reaction of K or Na and acetylene proved inferior in catalytic additions of acetylene and acetone, compared with additions employing the alkali metal hydroxides [6]. In this process the use of highly polar solvents, for example DMSO, *N*-methylpyrrolidone, ammonia, and HMPA, has proven optimum. It been suggested that the high solubility of acetylene in such media and putative hydrogen bonds between solvent and the terminal acetylene are relevant. In 1996, the use of potassium *tert*-butoxide to effect the deprotonation of terminal alkynes in DMSO was reported [7]. Addition of the resulting potassium alkynylides to aldehydes and ketones subsequently was shown to afford propargylic alcohols (Eq. 1).



Corey introduced the use of a 1:1 CsF/CsOH salt to effect the in-situ activation of trimethylsilyl alkyne and subsequent addition to aldehydes (Eq. 2) [8]. The use of catalytic quantities of CsOH to effect the addition of terminal acetylenes to ketones in DMSO/THF or THF has also been documented (Eq. 3) [9].



Although application and use of acetylenic potassium and organocesium reagents have inherent practical advantages related to cost and safety, stereochemical control with these reagents in additions to C=O electrophiles has, in gen-

eral, proven elusive. In contrast, the coordination chemistry of the d-block metals is considerably better understood and more facile to control. As such, the development of methods for generation of transition-metal acetylides that are sufficiently reactive to participate in C=O additions would offer advantages in the discovery and development of enantioselective methods for the preparation of propargylic alcohols from terminal acetylenes and aldehydes or ketones.

1.1.3

Enantioselective Addition of Terminal Alkenes to Aldehydes

Methods for the enantioselective addition of metal acetylides to aldehydes can be divided into two categories:

1. addition reactions with stoichiometric, preformed metalated terminal acetylenes, and
2. addition reactions with in-situ formation of the metal alkynylides in sub-stoichiometric amounts.

Asymmetric alkynyl additions to aldehydes by prior, separate generation of the alkynylides (e.g. dialkylzinc reagents) have recently been reviewed and are a topic of current research [10]. They will not be covered in the context of this chapter. Instead, in line with the theme of this book, this chapter will focus on the metalation of terminal alkynes by activation of the terminal C–H and the use of the corresponding metal acetylides in aldehyde and ketone addition reactions.

In 1999, Carreira identified Zn(II) as a metal that, like Ag(I) and Cu(I), is capable of effecting the metalation of terminal acetylenes under mild conditions. Thus, treatment of terminal alkynes with Zn(OTf)₂ and NEt₃ at room temperature led to the formation of zinc alkynylides (Eq. 4). The zinc salt and the amine base work in synergy to weaken the acetylenic proton, with the acetylene undergoing complexation to the Zn(II) center and the base effecting subsequent deprotonation (Fig. 1) [11].

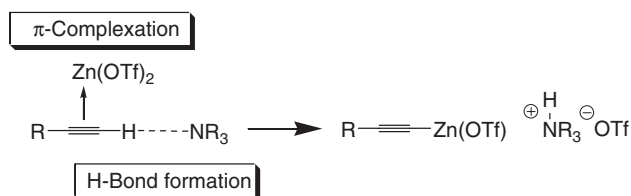


Figure 1. Proposed process for metalation of terminal acetylenes by Zn(II) and amine bases.

The proposed metalation process involving the formation of a putative zinc acetylide was substantiated by a series of infra-red spectroscopic studies (Fig. 2) [12]. The synergistic effect in the deprotonation event of the zinc salt

($\text{Zn}(\text{OTf})_2$) and amine base (e.g. triethylamine, Hünig's base) could be readily monitored by observation of the disappearance of the stretch corresponding to the terminal C–H bond of phenylacetylene. Consistent with a reversible metalation, reappearance of the terminal C–H stretch could be observed on stepwise addition of triflic acid. During treatment of phenylacetylene with either amine base or $\text{Zn}(\text{OTf})_2$ alone, no evidence of deprotonation was detected.

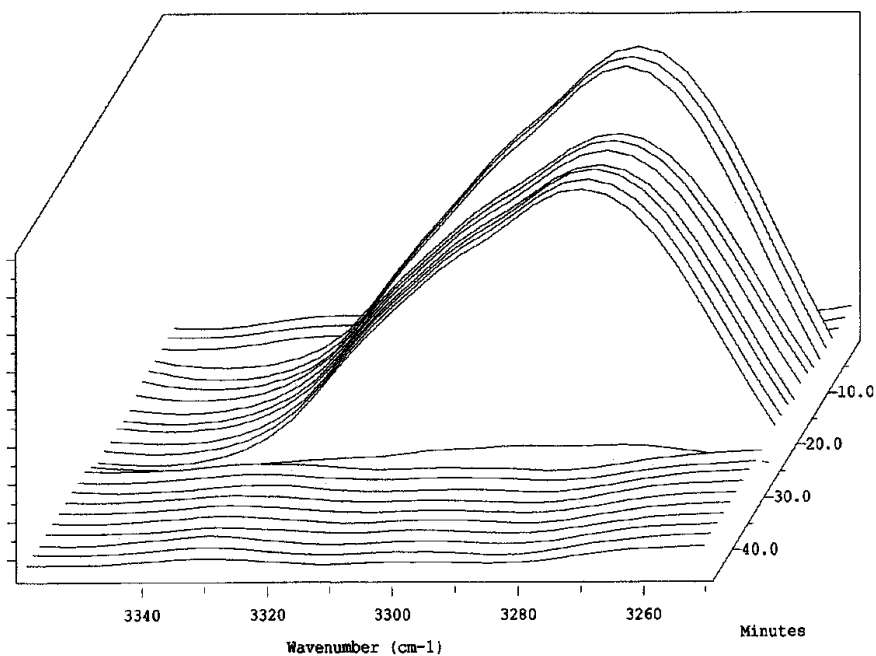
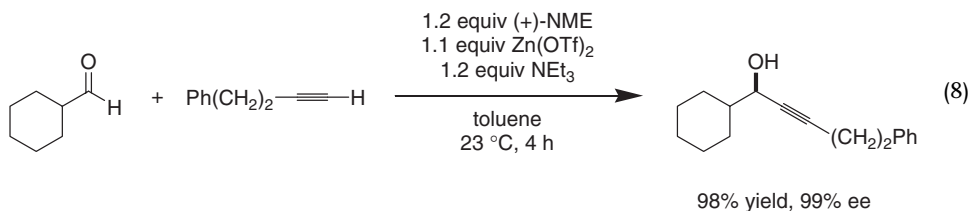
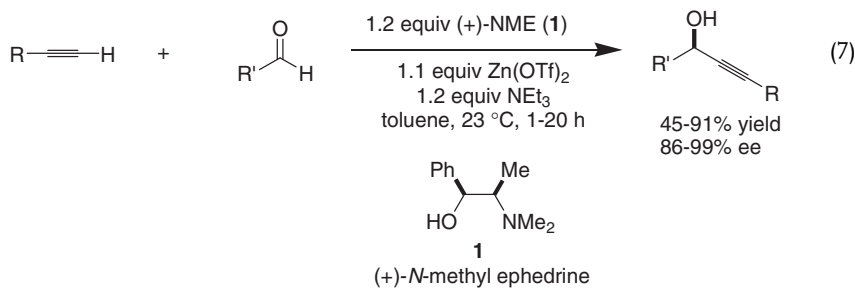
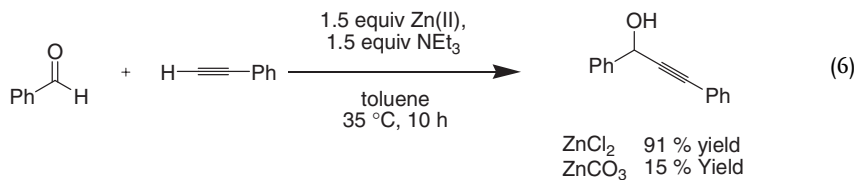
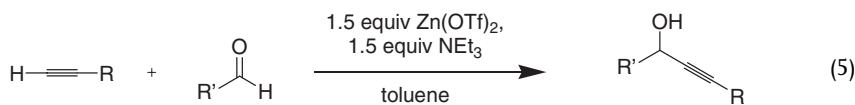


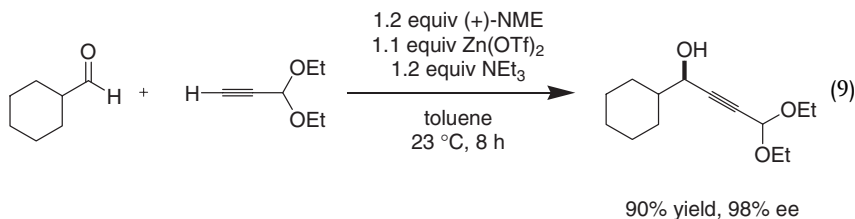
Figure 2. ReactIR spectra of the C–H stretch resonance signal of phenylacetylene in CH_3CN . Addition of Et_3N and subsequent addition of $\text{Zn}(\text{OTf})_2$ resulted in the disappearance of the terminal C–H resonance within 4 min.

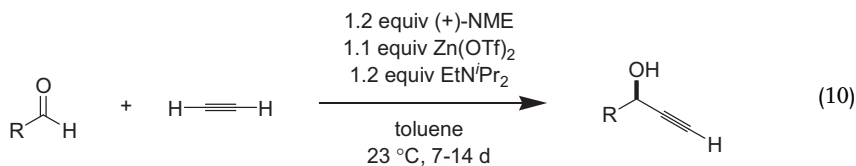
The new reactivity mode for the in-situ generation of metal alkynylides was exploited in addition reactions to aldehydes. Stoichiometric quantities of $\text{Zn}(\text{OTf})_2$ and NEt_3 or Hünig's base effected deprotonation of a number of alkynes which underwent smooth addition to various aldehydes to furnish the corresponding propargylic alcohols (Eq. 5) [13]. Subsequent studies revealed that apart from $\text{Zn}(\text{OTf})_2$ other zinc sources such as ZnCl_2 and ZnCO_3 could be used in this reaction (Eq. 6) [14].

Shortly after this initial success, the isolation of optically active propargyl alcohols in up to 99% ee could be effected by the use of stoichiometric amounts of (+)-*N*-methyl ephedrine (**1**) (Eq. 7). A wide range of aldehydes and acetylenes participate in this addition reaction affording the product alcohols in generally high yields, especially when using aldehydes that are α -branched (Eq. 8). Of additional importance, the reaction can be performed with functionalized alkynes, which

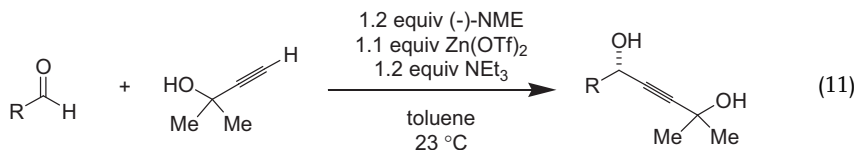


illustrates the mildness of the metalation conditions (Eq. 9). In further expanding the scope of the addition reaction, ethyne has been shown to yield products with high enantioselectivity (Eq. 10) [15]. Alternatively, 3-hydroxy-3-methylbut-1-yn (**2**) can be used as a convenient ethyne substitute (Eq. 11). Removal of the acetone protecting group on the acetylene can be conveniently accomplished under mild conditions (Eq. 12) [16].

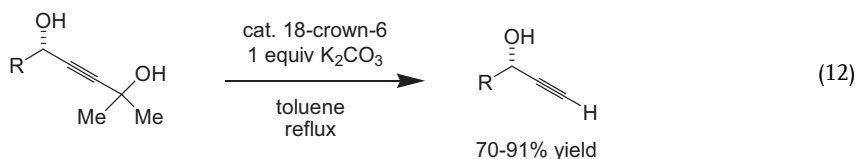




30–92% yield
91–98% ee

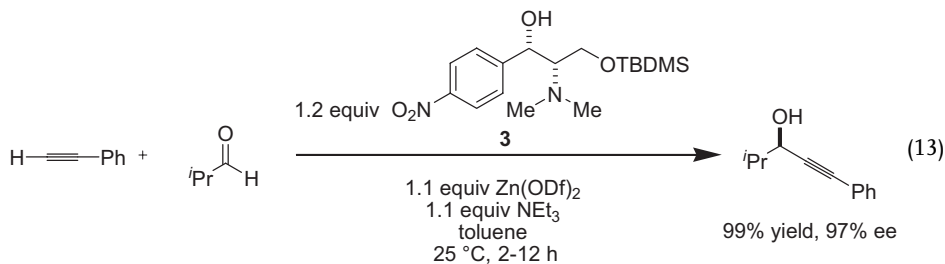


up to 97% yield
up to 99% ee

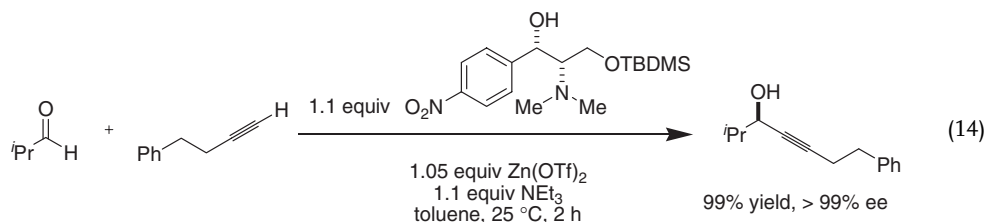


70–91% yield

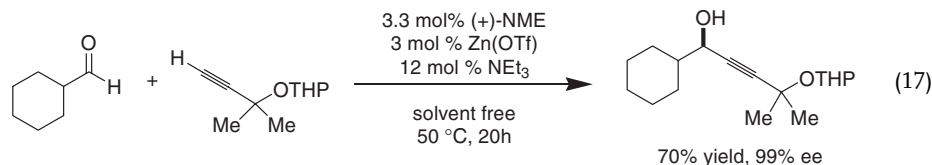
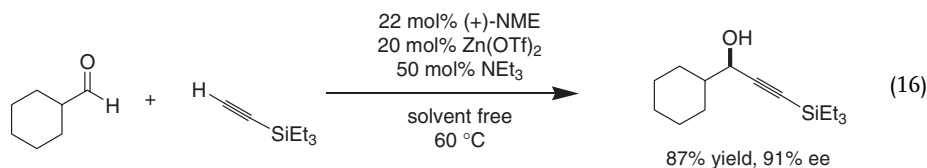
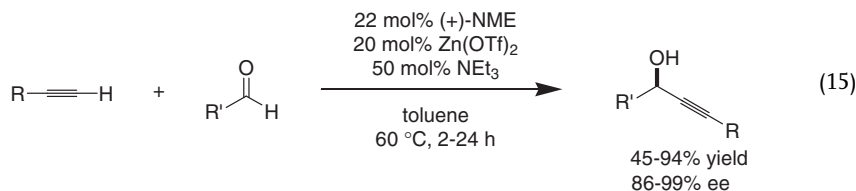
Jiang has expanded the Carreira method of alkyne addition to aldehydes to include other ligands and Zn(II) salts (Eq. 13) [17]. Thus use of stoichiometric quantities of Zn(II) difluoromethane sulfonate salt and (1*S*,2*S*)-3-(*tert*-butyldimethylsilyloxy)-2-*N,N*-dimethylamino-1-(*p*-nitrophenyl)propane-1-ol (**3**) in the addition reaction can afford propargylic alcohols in high ee. Difluoromethanesulfonic acid is prepared from 3,3,4,4-tetrafluoro[1.2]oxathietane; the amino alcohol has been used in the synthesis of chloramphenicol and is also readily accessible. Application of a combination of this same amino alcohol ligand with Zn(OTf)₂ has also been shown to afford products in high yield and ee in addition reactions (Eq. 14) [18].



99% yield, 97% ee



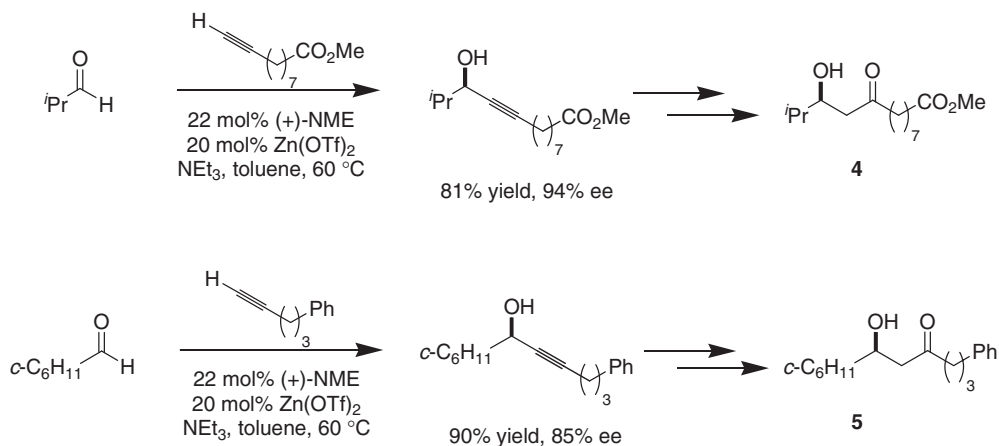
A catalytic version of the Zn(II)-mediated enantioselective addition of alkynylides to aldehydes was documented after the stoichiometric process [19]. Initially, the reaction was reported to proceed using 22 mol % *N*-methylephedrine, 20 mol % Zn(OTf)₂, and 50 mol % Et₃N to furnish the product alcohols in yields and enantioselectivity only marginally lower than in the original stoichiometric version (Eq. 15). The key difference between the stoichiometric and the catalytic procedures is the elevated temperature (60 °C) for the catalytic process. Because the reaction can also be conducted under solvent-free conditions, ensuring a process with a high atom economy and volumetric efficiency (Eq. 16). Under these conditions, the reactions can be conducted with substantially lower catalyst loading (Eq. 17) [13].



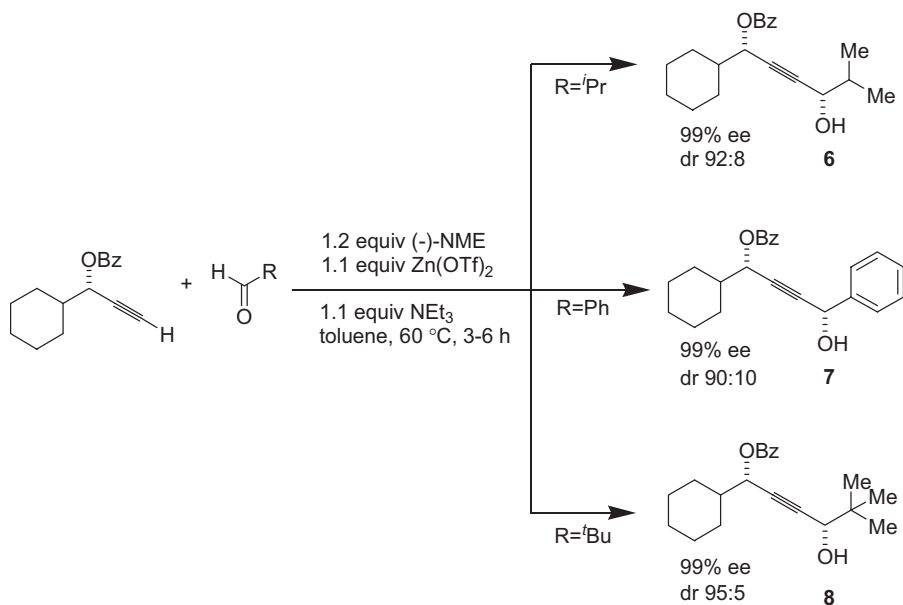
1.1.4

Applications

The methods described have already found numerous applications in the synthesis of building blocks and natural products. β -Hydroxy ketones **4** and **5** (Scheme 1) [20] and 1,4-diols **6–8** [21] are conveniently accessed, with high selectivity, by alkylation then hydroboration (Scheme 2).

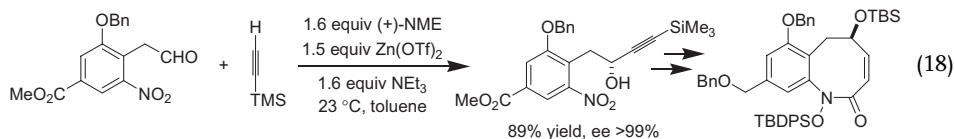


Scheme 1

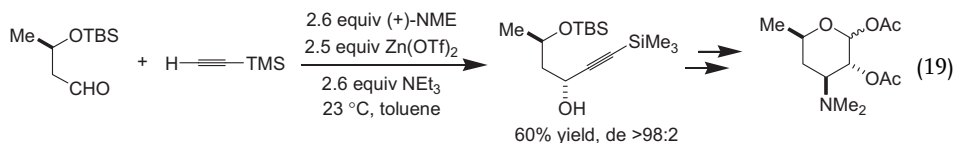


Scheme 2

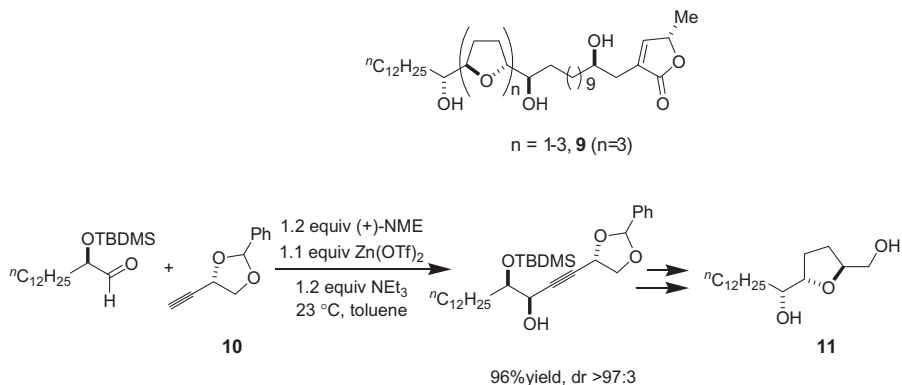
Trost has exploited the asymmetric alkyynylation of an α -unbranched acetaldehyde in an elegant synthesis of the core of the mitomycin analog FR900482 [22]. This is a remarkable example wherein an enolizable aldehyde participates in the addition reaction. It has been suggested that this is critical for the success of these substrates, because the aldehyde undergoes reversible enolization. (Eq. 18).



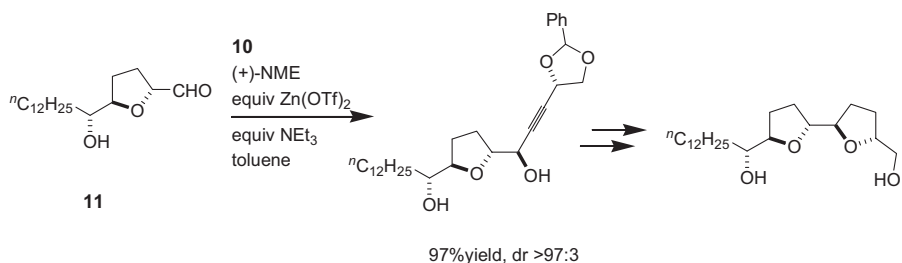
McDonald performed an asymmetric synthesis of D-desosamine, with high selectivity, by diastereoselective addition of TMS-acetylene to an α -unbranched aldehyde obtaining the propargylic alcohol [23]. The reaction proceeded in nearly 100 % diastereoselectivity albeit in moderate (60 %) yield (Eq. 19).



Tanaka has shown that in his synthesis of a variety of diastereomeric annonaceous acetogenins (**9**, Scheme 3) the carbinol stereocenter can be generated with predictable selectivity by reagent control of either enantiomer of the chiral ligand [24]. He applied this method in the total synthesis of murisolin (**9**, $n=1$), a member of family of over 350 natural polyketides isolated from various annonaceae plants (Scheme 4).

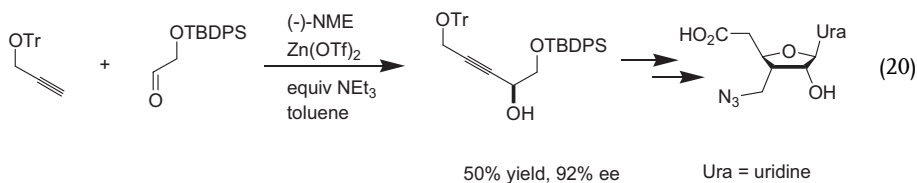


Scheme 3

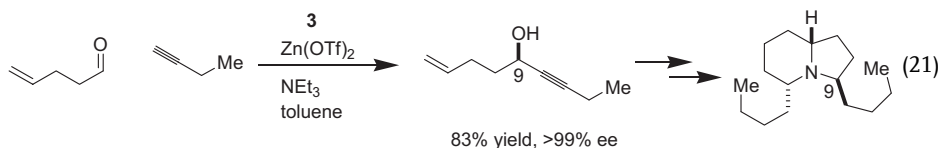


Scheme 4

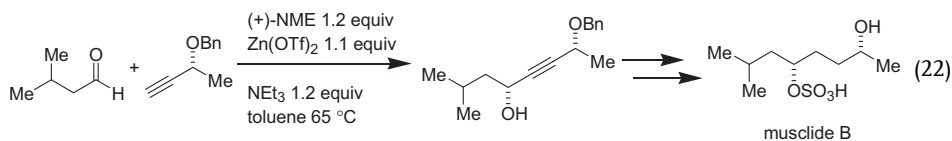
Rozner published a synthesis of 3',5'-C-branched nucleosides and used the addition of protected propargyl alcohol to an α -siloxyaldehyde to control absolute stereochemistry at C2' [25]. He noted that use of the bulky trityl and TBDPS protecting groups were essential for the reaction. In this respect the corresponding product could be isolated in only low yield (>10 %) when changing to MOM-protected propargyl alcohol and TBS-protected oxaldehyde (Eq. 20).



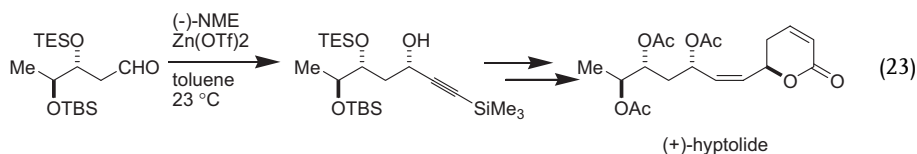
Smith has employed a related process using the ligand **3** developed by Jiang to obtain a chiral propargyl alcohol. This served as a key building block in an elegant synthesis of (-)-indolizidine **223AB** (Eq. 21) [26].



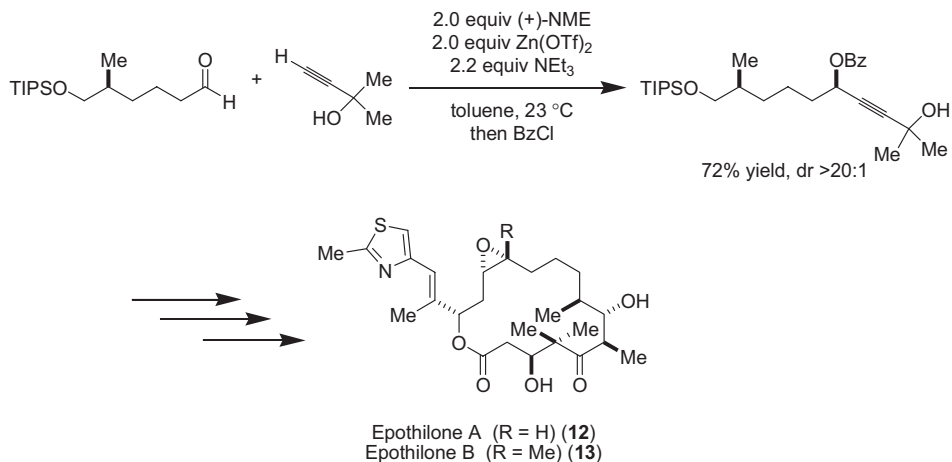
Ariza took advantage of the use of acetylides for preparation of unsymmetrical 1,4-diols, adopting it to the synthesis of the natural product musclide B [27]. He also showed for a number of different aldehydes that by correct choice of the enantiomeric ligand the diastereomeric, protected diols were accessible in 87:13 to 98:2 diastereoselective ratios (Eq. 22).



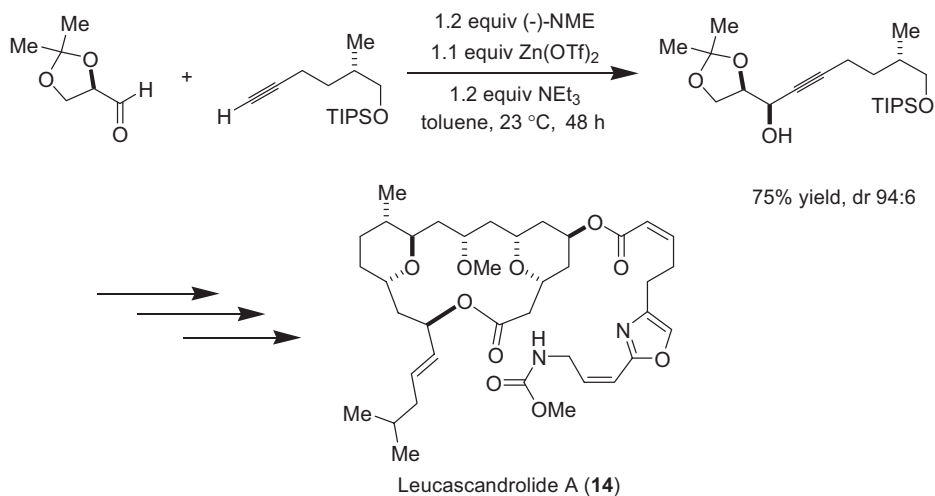
In a synthesis of (+)-hyptolide Marco exploited the Carreira procedure for alkylation of a β -silyloxy aldehyde to afford the product propargyl alcohol as a single isomer [28]. Subsequent semireduction of the alkyne furnished the requisite Z double bond to complete the synthesis (Eq. 23).



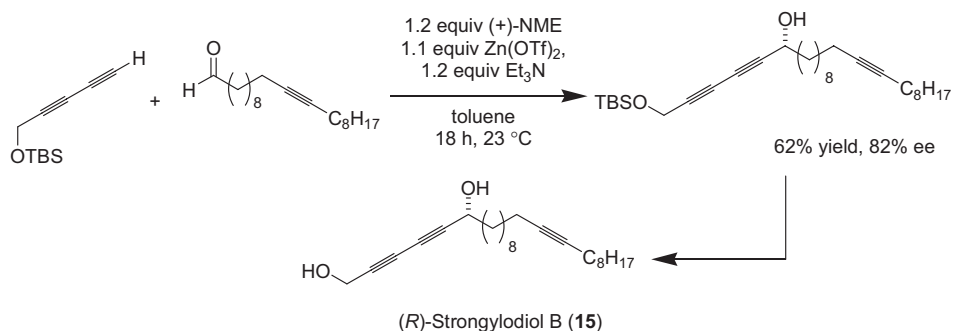
Carreira employed this method in the context of the total syntheses of the complex natural products epothilones A (**12**) and B (**13**) [29] and leucascandrolide (**14**) (Schemes 5 and 6) [30]. The synthesis of strongylodiol B (Scheme 7) expands the scope of the process to include the activation and asymmetric addition of 1,3-diynes such as **15** [31].



Scheme 5



Scheme 6



Scheme 7

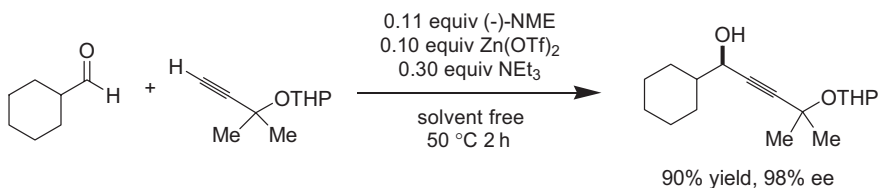
1.1.5

Conclusion

The use of terminal acetylenes for the synthesis of value-added compounds has several important advantages in contrast to the practice of modern synthetic chemistry. Two of the most prominent of these are that numerous terminal acetylenes are readily available as starting materials at low cost from commercial sources and that the product propargyl alcohols are amenable to a wide range of synthetic transformations. It is thus hardly surprising that addition of acetylenes to aldehydes was examined as early as the turn of the twentieth century. The metalation of terminal acetylenes is one of the simplest C–H-activation processes that can be executed. The discovery that this can be facilitated by a variety of different metal salts under mild conditions has been a boon to the subject. That the reactivity of these can be modulated to effect ligand-accelerated enantioselective additions to C=O also offers new opportunities for enantioselective synthesis of propargylic alcohols. Indeed, the mildness and utility of this new procedure are evident from the various applications in natural product and building block syntheses that have recently appeared.

Experimental

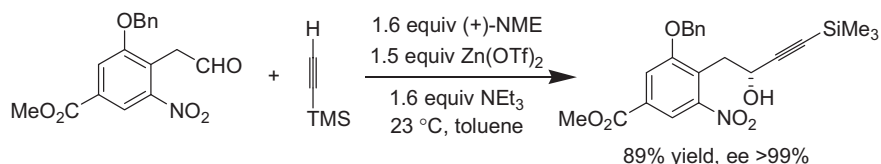
For example 1, see: Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687; Fässler R. Ph.D. Thesis, Swiss Federal Institute of Technology, Diss ETH No. 14936, Zürich, 2003.



An oven-dried *Schlenk* flask was charged with $\text{Zn}(\text{OTf})_2$ (545 mg, 1.50 mmol, 0.10 equiv) and evacuated under high vacuum (ca. 0.1 mbar). The salt was dried for 2 h at 120 °C, with stirring. The flask was cooled to ambient temperature, (–)-NME (296 mg, 1.65 mmol, 0.110 equiv) was added, and the solids were mixed with stirring for 30 min at ambient temperature. After purging the flask with argon, 2-(tetrahydropyranyloxy)-2-methyl-3-butyne (2.78 g, 16.5 mmol, 1.10 equiv) and NEt_3 (623 μL , 4.50 mmol, 0.30 equiv) were added, and the resulting mixture was vigorously stirred for ca. 20 min, cyclohexane carboxaldehyde (1.68 g, 15.0 mmol, 1.00 equiv) was added and the reaction mixture was warmed to 50 °C and stirred for 2 h at this temperature. After cooling to 23 °C, the reaction mixture was poured on to a stirred mixture of 20.0 mL sat. aq. NH_4Cl solution, 10.0 g ice, and 50.0 mL Et_2O . The phases were separated and the aqueous phase was extracted with diethyl ether (2 \times 60 mL). The combined organic layers were washed with sat. aq. NH_4Cl solution and brine, dried over MgSO_4 , filtered, and concentrated in vacuo. The residue was distilled by Kugelrohr distillation under high vacuum (0.03 mbar) to afford the propargylic alcohol in 90 % yield and 98 % ee (as determined by HPLC analysis of the 3,5-dinitrobenzoate ester; Chiralcel AD, 10 % i -PrOH in hexane, 254 nm) t_r minor = 25.7 min; t_r major = 49.5 min.

$[\alpha]_D^{23} +5.2^\circ$ ($c = 1.2$, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 5.04 (s, 1H), 4.18 (d, $J = 5.9$ Hz, 1H), 3.98–3.93 (m, 1H), 3.52–3.47 (m, 1H), 2.15 (br s, 1H), 1.89–1.67 (m, 7H), 1.59–1.43 (m, 5H), 1.53 (s, 3H), 1.49 (s, 3H), 1.32–1.01 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3) δ 96.1, 88.0, 84.0, 71.0, 67.0, 63.3, 44.2, 32.0, 30.5, 29.9, 28.6, 28.0, 26.4, 25.9, 25.8, 25.3, 20.5; FTIR (thin film) 3604, 3402, 3009, 2931, 2855, 1452, 1381, 1248, 1124, 1074, 1031, 996, 946, 868, 814 cm^{-1} ; MS (EI) 280.2 ($[\text{M}]^+$, <1), 265.3 ($[\text{M} - \text{CH}_3]^+$, <1), 161.2 (11), 96.0 (33), 95.1 (30), 85.1 (100), 83.1 (28), 69.1 (56), 55.1 (32); Anal. Calcd. for $\text{C}_{17}\text{H}_{28}\text{O}_3$: C, 72.82 %; H, 10.06 %. Found: C, 72.87 %; H, 9.91 %.

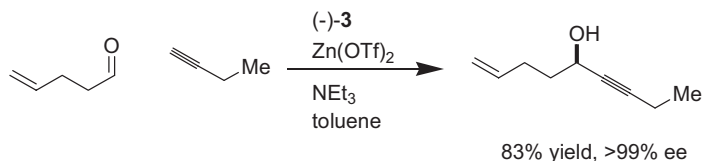
For example 2, see: Trost, B. M.; Ameriks, M. K. *Org. Lett.* **2004**, 6, 1745.



Triethylamine (492 mg, 677 μL , 4.86 mmol) was added at once to a mixture of zinc trifluoromethanesulfonate (1.656 g, 4.56 mmol) and (1*S*,2*R*)-(+)-*N*-methylephedrine (871 mg, 4.86 mmol) in toluene (10 mL). The resulting slurry was stirred at room temperature for 2 h. Trimethylsilylacetylene (477 mg, 687 μL , 4.86 mmol) was added at once, and the reaction mixture was stirred for an additional 45 min. The aldehyde (1.00 g, 3.04 mmol) was added at once, and the resulting red mixture was stirred at room temperature for 17.5 h. The reaction was quenched with saturated aqueous NH_4Cl , diluted with water, and extracted with EtOAc ($\times 3$). The combined organic extracts were dried (MgSO_4), filtered, and concentrated under reduced pressure to give an orange oil. The crude product was purified by flash

chromatography (SiO₂, 10 % EtOAc in pet ether to 20 % EtOAc in pet ether) to afford 1.158 g (89 %) of the target compound as a clear oil. The enantiomeric purity was determined to be >99 % by chiral HPLC analysis as compared with the racemic standard. Chiralcel OD at 23 °C, 1.0 mL min⁻¹ flow rate, 5 % iPrOH in heptane, λ = 254 nm, retention times for enantiomers: 17.54 (major), 21.26 (minor). $[\alpha]_D^{23} +1.21^\circ$ (*c* 1.16, CH₂Cl₂). *R_F* = 0.47 (25 % EtOAc in pet ether). IR (neat): 3486, 1728, 1538, 1293, 1250, 1063 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 8.09 (d, *J* = 1.5 Hz, 1H), 7.81 (d, *J* = 1.2 Hz, 1H), 7.41 (m, 5H), 5.22 (s, 2H), 4.70 (t, *J* = 6.8 Hz, 1H), 3.95 (s, 3H), 3.49 (d, *J* = 3.4 Hz, 1H), 3.46 (d, *J* = 1.7 Hz, 1H), 2.32 (d, *J* = 7.3 Hz, 1H), 0.13 (s, 9H). ¹³C NMR (75 MHz, CDCl₃): δ 164.9, 157.6, 151.6, 135.3, 130.3, 128.9, 128.5, 127.3, 125.8, 117.8, 115.7, 105.2, 90.2, 71.3, 61.8, 52.8, 33.9, -0.304. Anal. Calcd. for C₂₂H₂₅NO₆Si: C, 61.81; H, 5.89; N, 3.28. Found: C, 61.59; H, 6.00; N, 3.18.

For example 3, see: Smith, A. B., III; Dae-Shik, K. *Org. Lett.* **2004**, 6, 1493.



To a solution of Zn(OTf)₂ (4.20 g, 11.6 mmol, 1.10 equiv) and chiral ligand (–)-3 (4.10 g, 11.6 mmol, 1.10 equiv) in toluene (75 mL) was added TEA (1.62 mL, 11.6 mmol, 1.10 equiv) at ambient temperature. After 40 min, 4-butyne (3 mL) was transferred to the reaction mixture from a cold trap (–78 °C) via a cannula. After 15 min, the aldehyde (1.04 mL, 10.5 mmol) in toluene (5 mL) was added over 5 h by means of a syringe pump and stirred for an additional 7 h. The reaction mixture was poured into saturated aqueous NH₄Cl (100 mL), extracted with Et₂O (3 × 100 mL), washed with brine (50 mL), dried over MgSO₄, filtered, and concentrated in vacuo. Flash chromatography on silica gel, using diethyl ether–pentane (1:7) and then ethyl acetate as eluent, provide the target compound (1.20 g, 8.70 mmol, 83 % yield) as a colorless oil.

$[\alpha]_D^{23} -11.0^\circ$ (*c* 0.72, CHCl₃); IR (film) 3440 (s, br), 3078 (w), 2977 (s), 2938 (s), 2235 (m), 1641 (m), 1064 (m), 911 (m) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.84 (dddd, *J* = 17.0, 10.2, 6.7 and 6.6 Hz, 1H), 5.07 (dd, *J* = 17.1 and 1.5 Hz, 1H), 4.99 (dd, *J* = 10.3 and 1.4 Hz, 1H), 4.40–4.35 (m, 1H), 2.25–2.20 (m, 4H), 1.82–1.71 (m, 3H), 1.14 (t, *J* = 7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 137.87, 115.07, 87.15, 80.34, 62.21, 37.22, 29.46, 13.85, 12.35; high resolution mass spectrum *m/z* 137.0958 [(M – H)⁺; calcd for C₉H₁₃O: 137.0966]

1.2

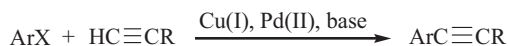
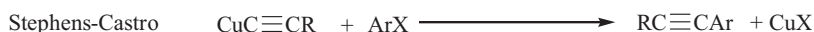
The Sonogashira Coupling Reaction

Herbert Plenio and Anupama Datta

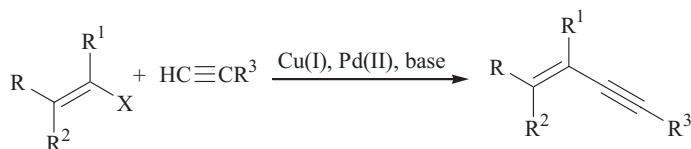
1.2.1

Introduction and Fundamental Examples

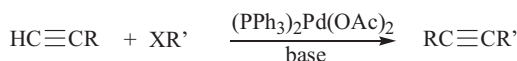
The first relatively efficient method available for bond formation between the sp -carbon of terminal alkynes and the sp^2 -carbon in aryl iodides was the Stephens–Castro coupling, involving reaction of preformed copper acetylides in pyridine at elevated temperatures to generate the respective aryl acetylenes [1]. In the early 1970s when the power of palladium-catalyzed cross-coupling reactions for the formation of C–C bond started to unfold, Sonogashira, Tohda, and Hagihara demonstrated a much more useful procedure for cross-coupling of terminal acetylenes and aryl halides (Scheme 1) [2, 3]. This reaction, which is now known as the Sonogashira coupling, requires catalytic amounts of Pd and Cu complexes and can be regarded as a major progress, because it removes the difficulties faced in the preparation and handling of copper acetylides and enables a wide range of functionalized 1-alkynes and aryl halides to be coupled. This work was first published in 1975, at the same time as Heck [4] and Cassar [5] reported related processes performed in the absence of copper co-catalyst, both of which require forcing conditions and can in fact be regarded as an extension to terminal acetylenes of what is now known as the Heck reaction.



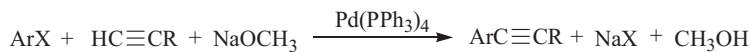
Sonogashira



Heck



Cassar



Scheme 1. Alkynylation reactions.

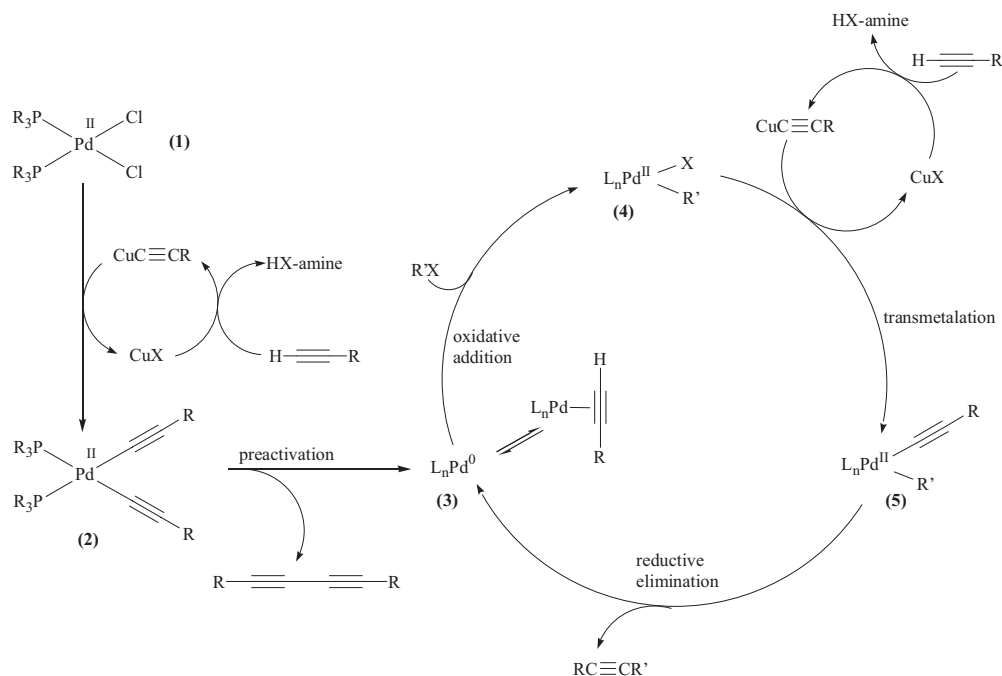
The Sonogashira reaction has finally emerged as the most widely used method for synthesis of substituted alkynes and reflects typical properties of Pd-catalyzed cross-coupling reactions, because it is technically simple, efficient, high yielding and tolerant towards a wide variety of functional groups [6]. In their very early publications Sonogashira et al. demonstrated carbon–carbon coupling between various acetylenes and iodoarenes, bromoalkenes or bromopyridines in the presence of catalytic amounts of $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ and CuI in diethylamine, leading to the formation of internal acetylenes. Since then, numerous modifications and improvements to this original procedure have been achieved by development of facile procedures, a wider array of substrates, and more active palladium catalysts for cross-coupling with deactivated arenes [7–9].

1.2.2

Mechanism

The mechanism of the Sonogashira reaction has not yet been established clearly. This statement, made in a 2004 publication by Amatore, Jutand and co-workers, certainly holds much truth [10]. Nonetheless, the general outline of the mechanism is known, and involves a sequence of oxidative addition, transmetalation, and reductive elimination, which are common to palladium-catalyzed cross-coupling reactions [6b]. In-depth knowledge of the mechanism, however, is not yet available and, in particular, the precise role of the copper co-catalyst and the structure of the catalytically active species remain uncertain [11, 12]. The mechanism displayed in Scheme 2 includes the catalytic cycle itself, the preactivation step and the copper mediated transfer of acetylide to the Pd complex and is based on proposals already made in the early publications of Sonogashira [6b].

$(\text{PPh}_3)_2\text{PdCl}_2$, which was originally employed by Sonogashira himself, is still the most commonly used palladium source in Sonogashira coupling. Alternatively, $\text{Pd}(\text{OAc})_2$, $(\text{CH}_3\text{CN})_2\text{PdCl}_2$, or Na_2PdCl_4 with at least two equivalents of a tertiary phosphine can also be used to form the catalytically active species in situ. With all Pd(II) salts the initial step leading to the catalytically active species is preactivation of the catalyst, i.e. reduction of Pd(II) to Pd(0), which is normally effected by reductive elimination from the cis-diacetylide **2** to form the respective butadiyne. Obviously the use of Pd(0) sources such as $\text{Pd}_2(\text{dba})_3$, $\text{Pd}(\text{dba})_2$, or $\text{Pd}(\text{PPh}_3)_4$ does not require such a preactivation step. The catalytic cycle probably involves neutral low-coordinate complexes, for example $[\text{L}_n\text{Pd}]$, even though an anionic $[\text{L}_n\text{PdX}]^-$ species is also considered [13]. In the past $[\text{L}_2\text{Pd}]$ was believed to be the most likely candidate for the catalytically active species [2], but more recent work from Hartwig has established that $[\text{LPd}]$ complexes also need to be considered [14]. The formation of low-coordinate Pd(0) species is favored in the presence of electron-rich and bulky phosphines and explains why very-high-activity catalysts are often formed with such ligands. In this context, the use of Pd(0) sources may not be favorable, because ligands, for example dba, needed to stabilize Pd(0) complexes also tend to coordinate and thus inhibit the catalytically active Pd species [15], as was also shown for the acetylenes (Scheme 2) [10].



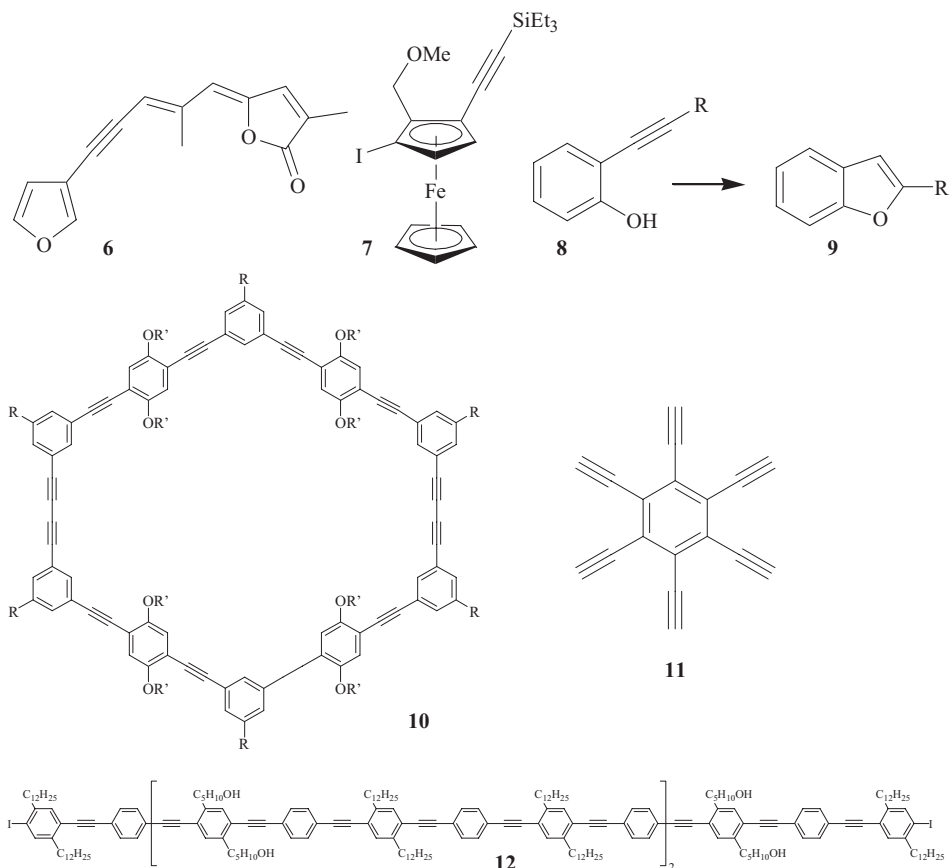
Scheme 2. Mechanism of the Sonogashira reaction for Pd/Cu-catalyzed cross-coupling of sp^2 -C halides with terminal acetylenes.

Subsequent oxidative addition of aryl or vinyl halides to $[\text{L}_n\text{Pd}]$ results in a $\text{Pd}(II)$ intermediate (4). The copper-supported alkynylation leads to the alkynylpalladium(II) derivative (5), which regenerates the catalytic species (3) by reductive elimination of the coupled products. The oxidative addition of the aryl halide to the $\text{Pd}(0)$ species is generally regarded as the rate-determining step in reactions with aryl bromides and chlorides. The general order of the overall reactivity of organic halides is: vinyl iodide > vinyl bromide > vinyl chloride = aryl iodide >> aryl bromide >> aryl chloride [6d]. The low reactivity of aryl chlorides is attributed to the strength of the C–Cl bond (bond dissociation energies for Ph-X ; $\text{X}=\text{Cl}$: 96 kcal mol^{-1} , $\text{X}=\text{Br}$: 81 kcal mol^{-1} , $\text{X}=\text{I}$: 65 kcal mol^{-1}) which render them reluctant to add oxidatively to $\text{Pd}(0)$ [16]. For a given halide X, substrates carrying electron withdrawing groups ortho or para to the aryl halide will react more readily, because the electron-deficient halides will undergo oxidative addition more easily [17].

1.2.3

Scope and Limitations

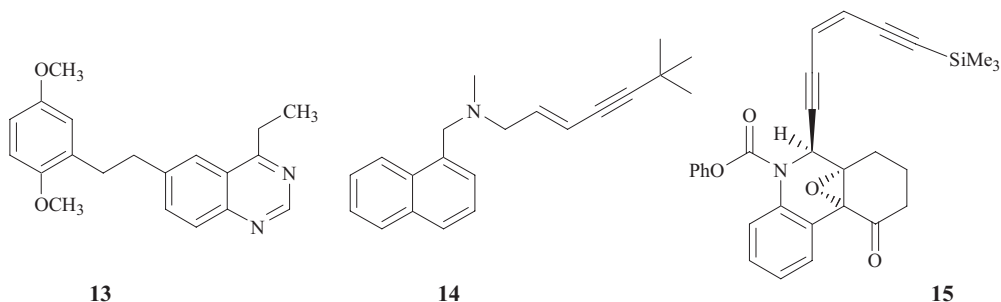
The Sonogashira cross-coupling reaction of terminal acetylenes with aryl or vinyl halides is a powerful tool for generation of carbon–carbon bonds between sp^2 - and sp -carbon. Numerous molecules of interest can be generated from a wide variety of aryl or vinyl halides (Scheme 3) [18–23].



Scheme 3. Examples of molecules generated by Sonogashira coupling reactions.

In the past decade the Sonogashira reaction has found many applications in the synthesis of scaffolds leading to molecular-scale electronic devices [24], dendrimers [25], estradiols [26], enediyne antibiotics [27], carbohydrate sensors [28], liquid crystals [29], and polymers [30]. The antimitotic agent **13** [31, 32], which inhibits the proliferation of human epidermal cells, is being developed for topical treatment of hyperproliferative skin disorders. A key step is a Sonogashira cross-coupling of an aryl halide and a heteroaryl halide (at a later stage the triple bond is

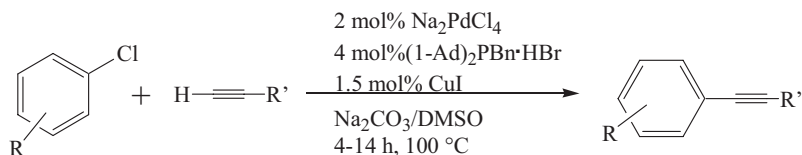
reduced to a C_2H_4 unit) (Scheme 4). Terbinafine **14**, which is an active ingredient of the Novartis broad-spectrum antimycotic Lamisil has been realized on an industrial scale by Sonogashira reaction [33]. An important step in the synthesis of terbinafine is the palladium-catalyzed coupling of a substituted vinyl chloride with *tert*-butylacetylene. The Sonogashira reaction is also applied in the Merck synthesis of MK-0462, a 5-HT₁₀ receptor agonist and potential antimigraine drug [34], in the DuPont synthesis of a DNA sequencing agent [35], and in the synthesis of a model system of dynemicin A (intermediate **15**) by Nicolaou [36, 37].



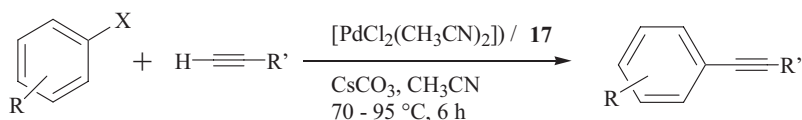
Scheme 4. Sonogashira reactions in the synthesis of 6-[2-(2,5-dimethoxyphenyl)ethyl]-4-ethylquinazoline **13**, terbinafine **14** and dynemicin A **15**.

Until the mid 1990s progress in the use of the Sonogashira coupling was mostly restricted to methods that could readily couple aryl iodides at room temperature [38, 39] and aryl bromides at elevated temperatures [40]. Aryl chlorides would be especially interesting as substrates because of their low price and the large variety of compounds which are commercially available. Hence, the development of catalysts with enhanced activity for cross-coupling reactions of aryl bromides and chlorides had to be addressed [41]. Some success has been reported using bulky, electron-rich phosphine ligands such as P^tBu_3 , by the groups of Buchwald and Fu [42] and Herrmann and Böhm [43]. These systems display excellent activity in cross-coupling reactions with aryl bromides at room temperature. Until fairly recently, however, only isolated examples were known of Sonogashira coupling of activated aryl chlorides [44, 45]. Effective cross-coupling of alkynes with aryl chlorides was reported by Eberhard et al., who used a phosphonito (PCP) palladium pincer complex **16** in the presence of $ZnCl_2$ [46]. Several aryl chlorides could be coupled with phenyl acetylene but these reactions required reaction for 24 h at 160 °C, a fivefold excess of the aryl chloride, and 10 to 100 mol% $ZnCl_2$ additive. The problems involved in the activation of aryl chlorides have essentially been solved recently through work of Plenio and Köllhofer [47] who reported a general and efficient procedure for Sonogashira coupling of both activated and deactivated aryl chlorides with terminal alkynes by use of a high-yielding catalyst based on $Na_2[PdCl_4]/PR_3/CuI$ ($PR_3 = (1-Ad)_2P^tBu$ or P^tBu_3) (Scheme 5). A variety of activated and deactivated chlorides were coupled with a variety of alkynes in excellent yield in toluene or DMSO at temperatures of 100 or 120 °C. Similarly, in a significant

improvement, Buchwald and Gelman for the first time demonstrated the Sonogashira coupling of aryl tosylates with terminal alkynes, using a catalyst prepared from phosphine **17** and $[\text{PdCl}_2(\text{CH}_3\text{CN})_2]$, a reaction which also works well with aryl chlorides (Scheme 6) [48].



Scheme 5. Palladium-catalyzed Sonogashira coupling of aryl chlorides according to Plenio and Köllhofer.

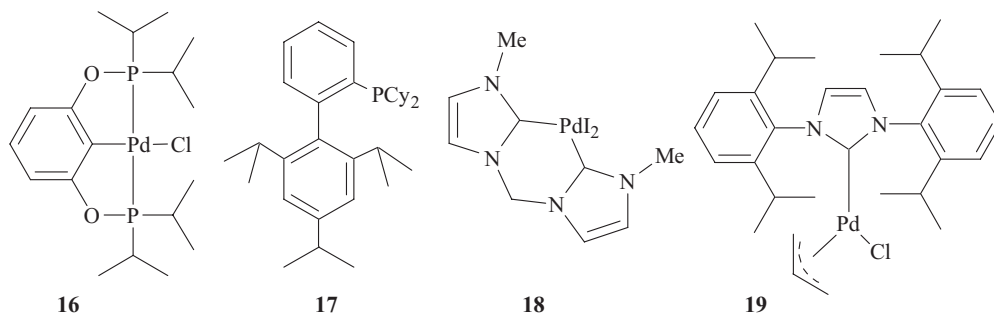


Scheme 6. Palladium-catalyzed Sonogashira coupling of aryl chlorides and tosylates according to Buchwald and Gelman.

Because the Sonogashira process is frequently associated with homo-coupling of the starting alkynes promoted by oxygen impurities in the presence of a copper co-catalyst, some effort has been devoted to the design of suitable catalysts for diminished alkyne dimerization. This was achieved either by using SiMe_3 -protected terminal acetylenes, which are deprotected during the coupling reaction, or by developing suitable copper-free procedures [49–53].

As an alternative to sterically hindered phosphines in the Sonogashira reaction, N-heterocyclic carbenes (NHC) have recently received increased attention [54–56]. Hermann was first to report the use of chelating ligand complex **18** in the Sonogashira reaction [57]. The effectiveness of NHC ligands in Sonogashira reactions was improved significantly by using the imidazolium system developed by Nolan and co-workers in combination with $\text{Pd}(\text{OAc})_2$ (Scheme 7) [58].

Initially, it was assumed that the presence of copper co-catalysts in the Sonogashira reaction is crucial for a highly efficient catalytic conversion. Nonetheless, there are alternatives and several other metal acetylides can be used instead [6a]. Blum et al. demonstrated that tetraalkynyl aluminates, prepared in situ from NaAlH_4 and terminal acetylenes, are useful in palladium-catalyzed cross-coupling reactions, because undesired homocoupling is avoided [59]. Fürstner [60] and Soderquist [61] introduced organoboron or trialkyloxyborate acetylides for sp-sp^2 carbon bond formation. Molander et al. [62] have recently demonstrated that cross-coupling with aryl halides and triflates can be efficiently carried out in the presence of potassium alkynyl trifluoroborates. Negishi et al. reported that the Pd-catalyzed alkynylation of alkenyl halides and triflates with zinc acetylides proceeds well even with alkynyl derivatives containing electron-withdrawing groups [63,



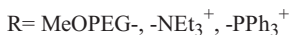
Scheme 7. Ligands and Pd complexes used for Sonogashira coupling.

64]. Wang et al. have discovered that ultrafine Ni powder in the presence of CuI, PPh_3 , and KOH promotes coupling of terminal alkynes with aryl and alkenyl iodides in high yields [65]. Recent developments have shown, moreover, that the use of co-catalysts (Cu, Zn, Al, etc.) to facilitate the formation of the acetylides is not always required and that cross-coupling reactions of acetylenes and aryl halides can be performed successfully with Pd-based catalysts alone, even with difficult substrates [48, 66]

Microwave heating has emerged as an interesting method to speed up chemical reactions frequently delivering high yields in just a few minutes as opposed to hours with conventional heating. A microwave-enhanced Sonogashira reaction in the presence of $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ and CuI was presented by Erdélyi and Gogoll and applied to the coupling of aryl iodides, bromides, triflates, and activated aryl chlorides with trimethylsilylacetylene [67]. Leadbeater has shown that Sonogashira-type reactions can even be performed with trace amounts of transition metals when applying microwave heating. This approach involves the use of water as solvent, poly(ethylene glycol) as phase-transfer agent, and NaOH, and enables reaction of terminal acetylenes with aryl iodides or bromides [68].

In homogeneously catalyzed reactions loss of the catalyst and contamination of the product with the catalyst metal can be a serious limitation. Developing efficient strategies for separation of the catalysts from the products is now recognized as an important subject in catalysis research [69]. One approach in this respect is the use of liquid–liquid biphasic solvent systems (biphasic catalysis). To enable this strategy a catalyst must be modified with a phase tag such that the solubility properties of this modified catalyst are determined by the phase tag whereas the catalytic properties are not affected [70, 71]. Example of catalysts with polar and nonpolar phase preferences are the Pd/PR_3 catalysts prepared from $\text{BnP}(1\text{-Ad})_2$ tagged with poly(ethylene glycol) (MeOPEG_{2000}) **20** or with soluble poly(*p*-methylstyrene) **21** (Scheme 8). A single batch of such catalysts can be used to efficiently couple aryl bromides or aryl chlorides and acetylenes in DMSO–*n*-heptane and cyclohexane–DMSO, respectively, over at least five consecutive reactions [72, 77]. The same polymer-enlarged catalysts have also been used in nanofiltration experiments and in continuous biphasic catalysis, with the polymer-tagged catalyst immobilized in a stationary solvent, with a flow of reactants passing through it, to

enable the conversion of a continuous feed of reactants into a product stream [73, 74]. The Sonogashira reaction has also been applied in a variety of other reaction media, for example aqueous phases [75], polar–nonpolar biphasic solvent mixtures [76–78], ionic liquids [79] and fluorous solvents [80] with the appropriate phase tags.



Scheme 8. Phase-tagged phosphines as ligands in Pd-catalyzed cross-coupling reactions.

Heterogeneous catalysts for Sonogashira coupling, comprising palladium complexes supported on organic resins [81, 82] or palladium deposited on inorganic supports, are also known. Most notable in this context is work from Choudary et al., who used a ligand-free heterogeneous layered double hydroxide-supporting nanopalladium catalyst which can activate aryl chlorides for Sonogashira reactions and can be reused for up to five consecutive cycles with almost constant activity [83]. A detailed mechanistic study relying on XPS and TGA-MS to elucidate the nature of surface transient organometallic intermediates, giving proof of elementary steps in the catalytic cycle, was carried out in the same group [84]. It is important to note in this respect that many supported Pd catalysts and some molecular catalysts function as a reservoir of soluble palladium nanoclusters, which promote the coupling reactions in solution and not on the support. Such nanoclusters are often redeposited on the solid support after the coupling reaction and can be used again with high activity when the morphology of the deposited material is suitable [85].

Experimental

General Procedure for Sonogashira Coupling of Alkynes and Aryl Chlorides According to Plenio and Köllhofer [47]

To a thoroughly degassed slurry of Na_2CO_3 (230 mg, 2.1 mmol) in dried toluene (3 mL) under argon atmosphere were added $\text{Na}[\text{PdCl}_4]$ (8.8 mg, 30 μmol , 2 mol%), PtBu_3 (12 mg, 60 μmol), CuI (4.4 mg, 23 μmol , 1.5 mol%), the chloroarene (1.5 mmol), and the alkyne (2 mmol). The mixture was heated to the respective reaction temperature (typically 100 °C) with vigorous stirring. After completion of the reaction (GC monitoring) and cooling to room temperature, the volatiles were removed in vacuo. The crude products are purified by chromatography on silica.

General Procedure for Coupling of Aryl Chlorides with Alkyl Acetylene According to Buchwald and Gelman [48]

An oven-dried Schlenk tube was evacuated and back-filled with argon (the cycle was performed twice) and then charged under a positive pressure of argon with $[\text{PdCl}_2(\text{CH}_3\text{CN})_2]$ (1.2 mg, 4.62 mmol, 1 mol%), phosphine **17** (6.6 mg, 14 mmol, 3 mol%), Cs_2CO_3 (391 mg, 1.20 mmol), followed by anhydrous acetonitrile (0.924 mL) and the aryl chloride (0.462 mmol). The slightly yellow suspension was stirred for 25 min. The alkyne (0.6 mmol) was then injected, the Schlenk tube was sealed with a Teflon valve, and the reaction mixture was stirred at the desired temperature for the indicated period of time. The resulting suspension was then left to reach room temperature, diluted with water (3 mL), and extracted with diethyl ether (4 × 4 mL). The combined organic layers were dried over MgSO_4 , concentrated, and the residue was purified by flash chromatography on silica gel to provide the desired product.

General Procedure for Coupling of Aryl Tosylates According to Buchwald and Gelman [48]

An oven-dried two-necked flask, equipped with reflux condenser, gas inlet/outlet, and rubber stopper, was evacuated and backfilled with argon (the cycle was performed twice) and then charged under a positive pressure of argon with $[\text{PdCl}_2(\text{CH}_3\text{CN})_2]$ (7.7 mg, 29.6 mmol, 5 mol%), phosphine **17** (42.4 mg, 89 mmol, 15 mol%), Cs_2CO_3 (0.87 g, 2.66 mmol), followed by propionitrile (1.8 mL) and the aryl tosylate (0.59 mmol). The slightly yellow suspension was stirred for 25 min at room temperature. (Efficient stirring of the reaction mixture and high purity of the starting tosylate are important for the transformation to be successful.) The reaction mixture was then heated to reflux and the alkyne (0.88 mmol diluted with 1 mL propionitrile) was injected slowly over the course of reaction (8 h) by means of a syringe pump. The reaction mixture was stirred for a further 2 h after addition was complete and the resulting suspension was left to reach room temperature, diluted with water (3 mL), and extracted with diethyl ether (4 × 4 mL). The combined organic layers were dried over MgSO_4 , concentrated, and the residue was purified by flash chromatography on silica gel to provide the desired product.

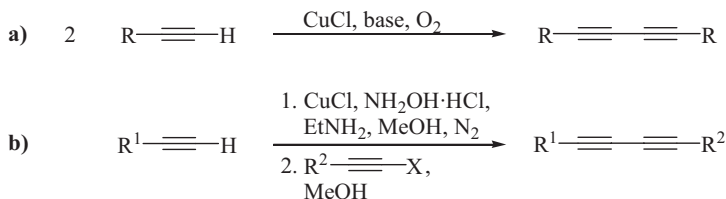
1.3**Glaser Homocoupling and the Cadiot–Chodkiewicz Heterocoupling Reaction**

Peter Siemsen and Beatrice Felber

1.3.1**Introduction and Fundamental Examples**

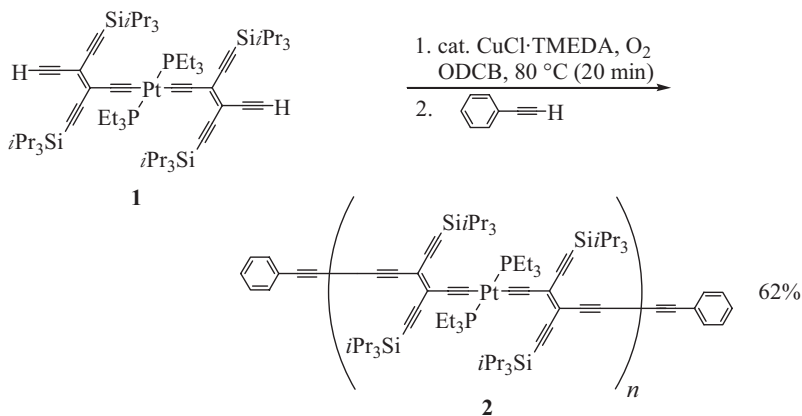
Homocoupling of terminal acetylenes first described by Glaser in 1869 [1] occurs in presence of a base, a copper(I) salt (usually CuCl) and dioxygen (Scheme 1a). Because of the widespread occurrence of di- and polyacetylenic structures in

natural products and the rapidly growing interest of material sciences in conjugated oligo- and polyacetylenes, the reaction has been investigated intensively and gained far-reaching applicability [2]. Besides progress achieved in the field of oxidative homocoupling processes, Chodkiewicz and Cadiot, in 1957, presented a nonoxidative procedure for achieving efficient copper-mediated heterocoupling of terminal alkynes with 1-haloalkynes in the presence of amines (Scheme 1b) [3].



Scheme 1. General description of (a) the oxidative Glaser-type homocoupling reaction and (b) nonoxidative Cadiot–Chodkiewicz heterocoupling (X = Br, I).

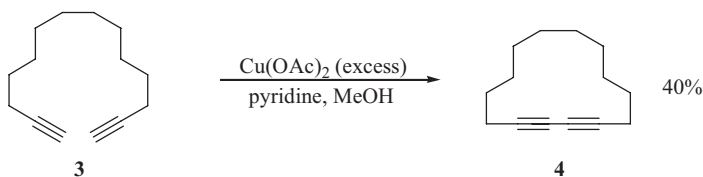
Of various homocoupling procedures derived from the original Glaser process that are still used today, Hay's procedure [4] using catalytic amounts of the bidentate complexing base TMEDA in polar solvents (e.g. acetone, dichloromethane or *o*-dichlorobenzene) is most utilized and is the method favored for preparing linear oligo- and polyacetylenes, as outlined in Scheme 2 [5].



Scheme 2. Preparation of polyacetylene **2** ($n \approx 32$) using the coupling procedure described by Hay. (ODCB: *o*-dichlorobenzene, TMEDA: *N,N,N',N'*-tetramethylethylenediamine.)

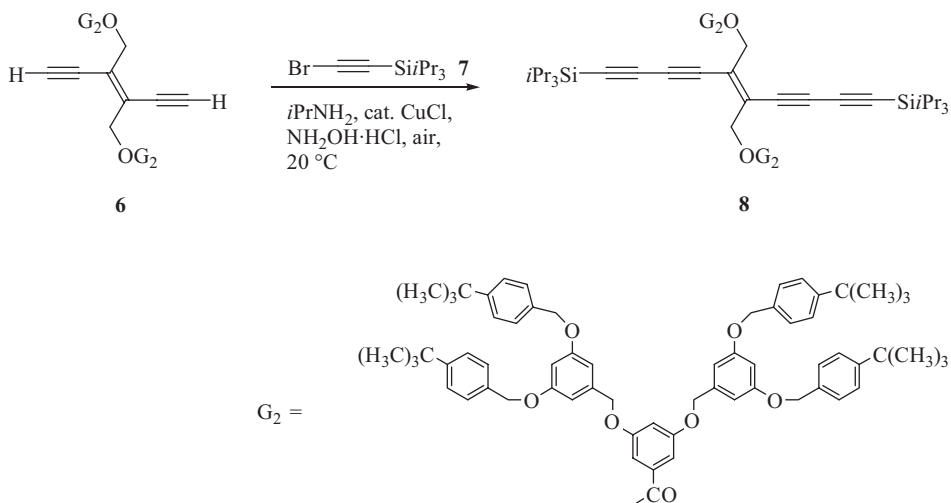
Although the Hay coupling has also been successfully used in the synthesis of cyclic oligoacetylenes (shown in the Section 1.3.3, Scheme 8) [6], for extended, macrocyclic oligoacetylenes the modification presented by Eglinton and Galbraith [7a] is quite often the method of choice[2]. Here copper(II) acetate must be used in large excess, most commonly dissolved in pyridine or mixtures of pyridine and methanol

(the cosolvent avoids precipitation of copper(I) reaction intermediates [7b]). Annulene syntheses developed by Sondheimer and co-workers [8] are a good example of the use of this procedure, particularly applicable to cyclizations (Scheme 3).



Scheme 3. Intramolecular acetylenic coupling in annulene synthesis described by Sondheimer [8] according to the method of Eglinton and Galbraith [7].

Whereas Glaser-type oxidative coupling opens efficient synthetic pathways toward symmetrical diynes, its performance in heterocoupling is poor. The latter may be accomplished by Cadiot–Chodkiewicz coupling of terminal alkynes with 1-haloalkynes (usually 1-bromoalkynes). The reaction is conducted in the presence of an amine and catalytic amounts of a copper(I) salt. Because, in contrast with the Glaser-type reactions described above, it follows a nonoxidative reaction mechanism, oxygen is not necessary – but needs often not to be excluded (Scheme 4) [9].



Scheme 4. Cadiot–Chodkiewicz heterocoupling under access of air. Reaction time 1 h; yield of heterocoupling product 64 % [9].

1.3.2

Mechanism

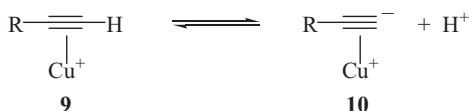
Although acetylenic homo- and heterocouplings have been widely used in different fields of organic synthesis, their exact mechanism is still obscure. Although several mechanistic hypotheses have been postulated for Glaser-type couplings, copper-catalyzed Cadiot–Chodkiewicz heterocoupling reactions have been little studied – largely because of the difficulty of kinetic studies, owing to the rapid reaction rates observed for the bromoalkynes commonly employed [2].

Because all currently known mechanisms of oxidative acetylenic homocouplings are very specific to single reaction conditions, e.g. pH or oxidation state of the used copper salt, this section summarizes the most reasonable mechanistic ideas proposed for the commonly utilized coupling procedures.

1.3.2.1 **Oxidative Homocoupling**

Studies by different research groups indicate that both Cu^+ and Cu^{2+} ions are involved in the coupling process [2]. Whereas copper(II) serves as the direct oxidizing agent, the role of copper(I) seems more versatile. Kinetic studies of acetylenic couplings in buffered solutions (Et_3N , HOAc, pyridine) in the presence of copper(I) and copper(II) salts showed copper(I) ions to play no role in the reaction, except that of an intermediate electron carrier [10a, b]. For couplings with mixtures of CuCl and CuCl_2 in non-buffered pyridine, however, it was found that copper(I) is indeed directly involved in the oxidative coupling process [10c]. The occurrence of higher-order copper(I)–copper(II)–ethynyl complexes in the rate-limiting step of the reaction has been proposed [10e], but not yet proven.

A very reasonable role of copper(I) in the coupling process seems to be intermediate formation of non-reactive copper– π -complexes. Coordination of cuprous ions activates the corresponding alkyne units toward deprotonation (Scheme 5).

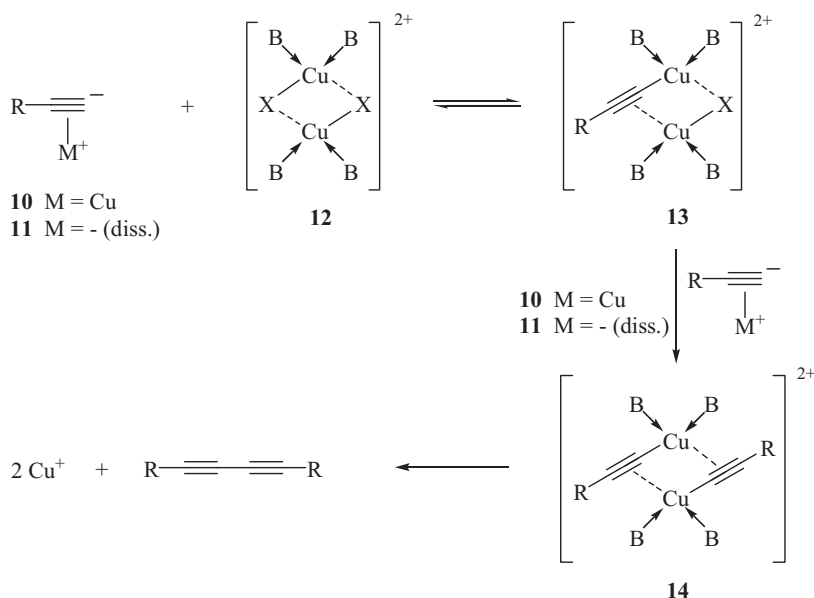


Scheme 5. Acetylene activation by π -complex formation between Cu^+ and the triple bond, postulated by Bohlmann et al. [10f].

This activation process can be assumed to be the initial step in the formation of dinuclear copper(II) acetylide complexes, as first proposed by Bohlmann and co-workers 40 years ago (Scheme 6) [10f]. Deprotonated alkyne units **11** (or the corresponding π -complexes **10**) generated therein, stepwise displace the negatively charged counter ions of copper(II) salt dimers (**12**). The dinuclear copper(II) acetylide complex which finally results (**14**) collapses to the coupled product under reductive elimination of copper(I). The existence of higher-order copper acetylide

complexes according to **13** and **14** has recently been demonstrated in the solid state [10g], whereas their presence in solution has not yet been proven.

It must be emphasized that current mechanistic understanding of copper-mediated oxidative acetylenic couplings is unsatisfactory. Several studies have shown the strong dependency of the mechanism on the experimental setup, suggesting highly complex coherences and interactions. Nevertheless, the mechanistic idea of Bohlmann et al. described above still provides the most accepted picture for Glaser-type oxidative acetylenic homocouplings.

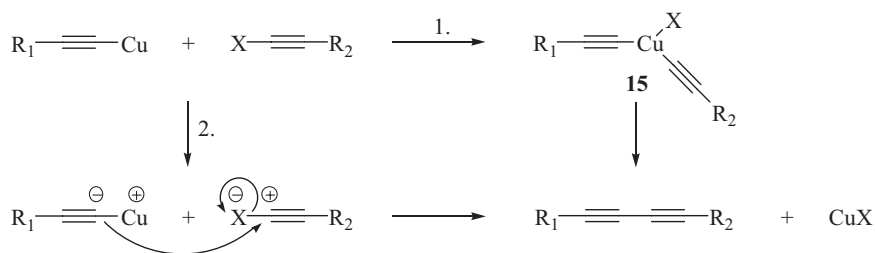


Scheme 6. The mechanistic proposal of Bohlmann et al. shows dimeric copper acetylides as key intermediates in copper-mediated acetylenic coupling (B = N-ligand, e.g. pyridine; X = Cl[−], OAc[−]) [10f].

1.3.2.2 Nonoxidative Heterocoupling

As already mentioned, there have been few mechanistic examinations of the copper-catalyzed Cadiot–Chodkiewicz heterocoupling reaction. Kinetic studies with the less reactive chloroalkynes [11a] have led to the assumption, shown in Scheme 7, that coupling between alkynes and haloalkynes proceeds through initial formation of copper(I) acetylides, probably formed by an acetylenic activation process similar to that described above for oxidative homocouplings. Subsequently, two reaction pathways may be reasonable:

1. Oxidative addition of the copper(I) acetylide to the alkynyl halide with formation of a copper(III) intermediate (**15**), giving the corresponding diacetylene by reductive elimination [11a].
2. Nucleophilic addition without change of the oxidation state, similar to couplings of alkynylmagnesium halides [11b].



Scheme 7. Mechanisms assumed for the Cadiot–Chodkiewicz heterocoupling ($X = Cl, Br$) [11].

Altogether, mechanistic understanding of both coupling processes, oxidative and non-oxidative, still requires much work. Improvements here may be promising for development of new coupling methods, enriching the already wide scope of acetylenic coupling reactions.

1.3.3

Scope and Limitations

Glaser-type homocouplings and Cadiot–Chodkiewicz heterocouplings have been applied to the synthesis of numerous aliphatic and aromatic diynes, as highlighted in a recent review [2]. Both methods are highly tolerant of a large variety of functional groups. Their synthetic capacity has been impressively demonstrated in the synthesis of the conjugated organic oligomers and polymers, presented in this section.

1.3.3.1 Oxidative Homocouplings of Tetraethynylethene Derivatives

Controlled Glaser–Hay coupling of platinum-bridged tetraethynylethene complex **1** rendered the synthesis of monodisperse, soluble oligomers up to the hexamer with a length of 12 nm, and a soluble polymer (**2**) with an average of approximately 32 repeat units and a remarkably narrow molecular weight distribution [5, 12]. Apart from the concentration of starting material, yield and ease of isolation of the single coupling products are strongly dependent on reaction conditions, as solvent, temperature, and time of addition of the end-capping agent phenylacetylene (Table 1).

The high coupling performance, apparent from total yields of isolable coupling products of 60–70 %, has also been found for the dimerization of tetraethynylethane derivative **17** to the cyclic diastereoisomers *syn*-**18** and *anti*-**18** (Scheme 8) [6].

Despite the high turnover rates of Glaser-type couplings, their applicability to the synthesis of macro-molecular structures is limited by two points:

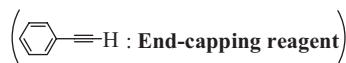
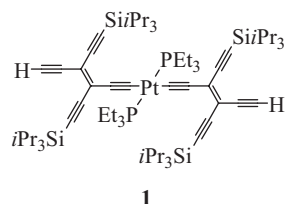
1. Because of the complex mechanism of these reactions, not yet sufficiently understood, directed synthesis of single monodisperse oligomers by end-capping polymerization of bis-protected acetylenes is not yet very effi-

cient. Mixtures of oligomers are usually obtained and the isolation of these will always be limited by the performance of current separation techniques.

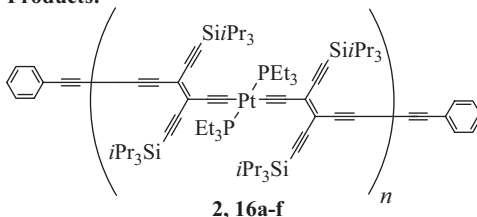
2. Formation of macrocyclic di- and oligoacetylenes in acceptable yields is rendered more difficult, because of the poor selectivity of Glaser-type couplings.

Table 1. Oligomerization and polymerization of compound **1** by Glaser–Hay coupling. Catalyst formation: CuCl, TMEDA, and O₂ in 1,2-dichlorobenzene [5, 12]. The reaction was performed in the presence of molecular sieves (4 Å). If PhC≡CH was available immediately at beginning of the coupling process (procedure C) an equal amount was added again 1 h before the end of the reaction. (*t_r* is the total reaction time and *t_{add}* is the time until addition of the end-capping reagent.)

Substrates:



Products:



	Solvent	<i>T</i> [°C]	<i>t_r</i> [h]	<i>t_{add}</i> [min]	<i>n</i>
(A)	<i>o</i> -C ₆ H ₄ Cl ₂	80	2.3	20	~32 (2 , 62%)
(B)	<i>o</i> -C ₆ H ₄ Cl ₂	80	2	10	1 (16a , 17%), 2 (16b , 12%), 3 (16c , 20%), 4 (16d , 13%), 5 (16e , 4%), 6 (16f , 1%)
(C)	CH ₂ Cl ₂	20	12	0	1 (16a , 56%), 2 (16b , 9%), 3 (16c , 4%)



71 % [6].

Cadiot–Chodkiewicz Reaction

method – especially for more reactive substrates.



Scheme 9. Side-reaction observed in Cadiot–Chodkiewicz couplings (X = I, Br) [11a].

Where applicable, this disturbing process can be suppressed by addition of amines and employing copper(I) and haloalkyne in reduced concentrations [11a, 13]. Thus, heterocouplings are frequently complicated for acetylenes of poor stability.

Although palladium-catalyzed processes have also achieved improvements in the field of acetylenic coupling [2], the Glaser–Hay and Cadiot–Chodkiewicz copper-mediated methods still remain the most used. Further mechanistic investigations seem to be necessary, to overcome the limitations of the existing procedures, mainly poor selectivity and predictability.

Experimental

Oxidative homocoupling: Glaser–Hay polymerization of compound 1 [5] – α,ω -Bis[phenylethynyl]poly[trans-bis{(Z)-4-ethynyl-6-(triisopropylsilyl)-3-[(triisopropylsilyl)ethynyl]-hex-3-ene-1,5-diynyl}bis(triethylphosphane)platinum(II)] (2)

A mixture of 1 (100 mg, 77 μ mol) and molecular sieves (4 Å) in 1,2-dichlorobenzene was heated to 80 °C. Under a stream of O₂ a solution of Hay catalyst (prepared by stirring CuCl (8.4 mg, 85 μ mol) and TMEDA in 1,2-dichlorobenzene (2 mL) under a stream of O₂ for 30 min at 20 °C) was added. After stirring for 20 min at 80 °C, PhC \equiv CH (176 μ L, 1.56 mmol) was added and the mixture stirred for 2 h at that temperature. PhMe (50 mL) was added, and the mixture was extracted with saturated aqueous NH₄Cl solution (2 \times 25 mL) and saturated aqueous NaCl solution (50 mL). Filtration over silica gel and evaporation gave a red-brown precipitate which was purified by GPC (Bio-Beads S-X1, PhMe [12]) to give 2 (62 mg, ~62 %) as a solid containing traces of 1,4-diphenylbuta-1,3-diyne which could not be removed by means of three GPC separations. ¹H NMR (CDCl₃, 500 MHz): δ = 0.83–1.35 (br s), 1.91–2.14 (br m), 7.27–7.44 (m), 7.46–7.49 (m); IR (CHCl₃): ν = 3011 (w), 2944 (m), 2867 (m), 2356 (w), 2322 (w), 2067 (s), 1600 (s), 1489 (m), 1461 (m), 1183 (m), 1017 (w), 917 (w), 883 (w), 700 (s), 689 (s); UV–visible (CHCl₃): λ_{max} (ϵ) = 489 (sh, 90 100), 446 (127 300), 423 (105 900), 305 (sh, 77 300), 294 (81 400). (ϵ calculated for polymer with 32 monomeric repeat units.)

Cadiot–Chodkiewicz heterocoupling: coupling of compounds 6 and 7 [9] – [(E)-1,10-Bis(triisopropylsilyl)dec-5-ene-1,3,7,9-tetrayne-5,6-diyl]dimethylene Bis{3,5-bis[3,5-bis[[4-(tert-butyl)benzyl]oxy]benzyl]oxy}benzoate} (8)

A solution of 6 (376 mg, 0.18 mmol) and 7 (198 mg, 0.75 mmol) in THF (8 mL) was cooled to 0 °C. Propan-2-amine (2 mL), CuCl (0.2 g, 0.20 mmol), and NH₂OH · HCl (0.02 g, 0.28 mmol) were added and the mixture was stirred for 1 h at 20 °C in the air. Saturated aqueous NH₄Cl solution was added, and the organic phase was extracted with CH₂Cl₂. Column chromatography (SiO₂, hexane–CH₂Cl₂ 1:1 \rightarrow 1:2) afforded 8 (293 mg, 64 %) as a pale yellow solid with m.p. 84 °C. ¹H NMR (CDCl₃, 200 MHz): δ = 1.04 (s, 42 H), 1.34 (s, 72 H), 5.02 (s, 24 H), 5.29 (s, 4 H), 6.61 (t, J = 2.3 Hz, 4 H), 6.72 (d, J = 2.3 Hz, 8 H), 6.82–6.83 (m, 2 H), 7.35–7.46 (m, 36 H); ¹³C NMR (CDCl₃, 50.3 MHz): δ = 11.16, 18.41, 31.23, 34.47, 64.40, 69.95, 70.21, 88.55, 89.41, 95.29, 101.70, 106.43, 107.63, 108.55, 125.56, 127.63,

129.70, 131.63, 133.79, 138.77, 151.13, 159.88, 160.42, 165.88; MALDI-TOF-MS (9-nitroanthracene): 2451 ($[M + Na]^+$). Anal. calc. for $C_{160}H_{192}O_{16}Si_2 \cdot H_2O$ (2445.49): C 78.58, H 8.00, found: C 78.49, H 7.83.

1.4

Dimerization of Terminal Alkynes

Emilio Bustelo and Pierre H. Dixneuf

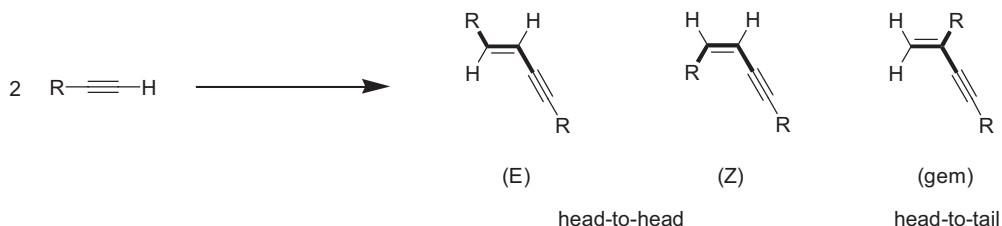
1.4.1

Introduction and fundamental examples

One of the most challenging topics in organic synthesis is the development of new catalytic systems which efficiently promote the selective formation of carbon–carbon bonds and combine several simple molecules into one useful product only. The simple catalytic dimerization of alkynes is atom-economic and straightforward method for synthesis of a set of versatile functional products. Among these, the preparation of *conjugated enynes* by direct coupling of two terminal alkynes enables easy access to important building blocks in organic synthesis. In particular, the regio- and stereoselective head-to-head dimerization of 1-alkynes is of special importance, because the resulting 1,3-enynes are key units found, for example, in a variety of naturally occurring antibiotics [1, 2]. Furthermore, the dimerization of acetylene itself, catalyzed by an alkynylcopper derivative, enables industrial access to but-1-en-3-yne and to neoprene rubber [3].

1.4.1.1 Simple Dimerization of Alkynes

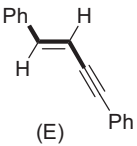
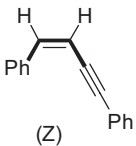
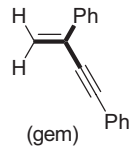
The synthetic application of the direct coupling of two acetylene units was initially limited by the formation of mixtures of regio (head-to-head and head-to-tail) and stereo (*E/Z*) isomers, and preference for trimerization processes [4]. During recent years, however, increased regio and stereochemical control has been achieved by the appropriate choice of catalyst. For example, conjugated polymers with enriched (*E*), (*Z*), or *gem*-vinylene linkages are selectively obtained by the use of suitable Pd, Ru, or Rh catalysts, respectively [5].



Scheme 1. Linear and branched enyne isomers from dimerization of alkynes.

The catalytic dimerization of alkynes has led to the development of a variety of catalysts by new combinations of transition metals and ligands, and to a better understanding of the processes and mechanism involved, leading to improvement of selectivity and scope. In Table 1 the most relevant catalysts are compared with regard to phenylacetylene dimerization. The nature of the terminal alkyne has also a marked effect on the outcome of this reaction.

Table 1. Selectivity of phenylacetylene dimerization by some transition metal catalysts.

Catalyst ^a	Yield	 (E)	 (Z)	 (gem)
Pd(OAc) ₂ /TDMPP [4, 6]	62 %	–	–	100
Pd(OAc) ₂ /IMes.HCl/Cs ₂ CO ₃ [7]	98 %	97	3	–
[(π-allyl)PdCl] ₂ /TDMPP/Et ₂ NH [8]	70 %	100	–	–
(PP ₃)Ru(C≡CPh) ₂ /NH ₄ PF ₆ [9]	80 %	5	84	–
Cp [*] Ru(PCy ₃)H ₃ [10]	86 %	10	90	–
Cp [*] Ru(PMe ₃)H ₃ [10]	82 %	90	10	–
TpRuCl(PPh ₃) ₂ [11]	98 %	91	6	–
RuCl ₂ (P ⁱ Pr) ₂ (=C=CHPh) [5]	>99 %	1	96	3
[Rh(PMe ₃) ₂ Cl] ₂ [12]	> 99 %	–	–	100
[Me ₂ Si(C ₅ Me ₅)(NAr)Lu(μ-CCR)] ₂ [13]	> 99 %	–	>99	–

^a TDMPP = P[(2,6-OMe)₂C₆H₃]₃, IMes = 1,3-dimesitylimidazolium, PP₃ = P(CH₂CH₂PPh₂)₃, Tp = trispyrazolylborate, Cp^{*} = C₅Me₅

Palladium catalysts enable the dimerization of functional alkynes with selective head-to-tail coupling in the presence of bulky phosphine ligands, for both homo-coupling of terminal alkynes or cross-coupling of mono and disubstituted alkynes [4, 6]. On the other hand, a palladium/imidazolium system gives linear (*E*)-enyne as the predominant products [7].

Mononuclear ruthenium complexes have become useful catalysts, not only because they can have high regio- and stereoselectivity but also because their catalyzed reactions rely on an elucidated mechanism. This true for the *cis*-dihydride (PP₃)RuH₂ complex, a catalyst precursor for the selective head-to-head dimerization of phenylacetylene to the corresponding (*Z*)-enyne, via bis(alkynyl) active spe-

cies [9]. Ruthenium hydride complexes such as $\text{Cp}^*\text{Ru}(\text{PR}_3)_3\text{H}_3$ are also versatile catalysts, for which selectivity has been achieved by modulating both the catalyst and the alkyne substrates [10]. On the other hand, $\text{TpRuCl}(\text{PPh}_3)_2$ [11] and $\text{Cp}^*\text{RuCl}(\text{C}\equiv\text{CHPh})(\text{PPh}_3)$ [14] catalysts lead to the *E* isomer of 1,3-enynes. A *Z*-selective head-to-head dimerization of aliphatic alkynes by thiolate-bridged diruthenium complexes has also been reported for aliphatic and functionalized alkynes [15].

The *rhodium–trimethylphosphine system* is remarkable because it catalyzes the dimerization of aryl substituted acetylenes, yielding the scarce branched head-to-tail coupling product [12]. The *iridium* species generated from $[\text{Ir}(\text{COD})\text{Cl}]_2$ and phosphine selectively yields linear (*E*) or (*Z*) enynes from silylalkynes, depending on whether triaryl or tripropylphosphines, respectively, are used [16].

Lanthanide metallocene compounds are also active catalysts for the dimerization of terminal alkynes, giving predominantly the linear head-to-head enyne dimer with a double bond of *E* configuration [17]. In recent years, however, novel organo-lanthanide [13] and organoactinide [18, 19] systems have shown their ability to produce, with high selectivity, *Z* and geminal enyne products, respectively.

1.4.1.1.1 Mechanism

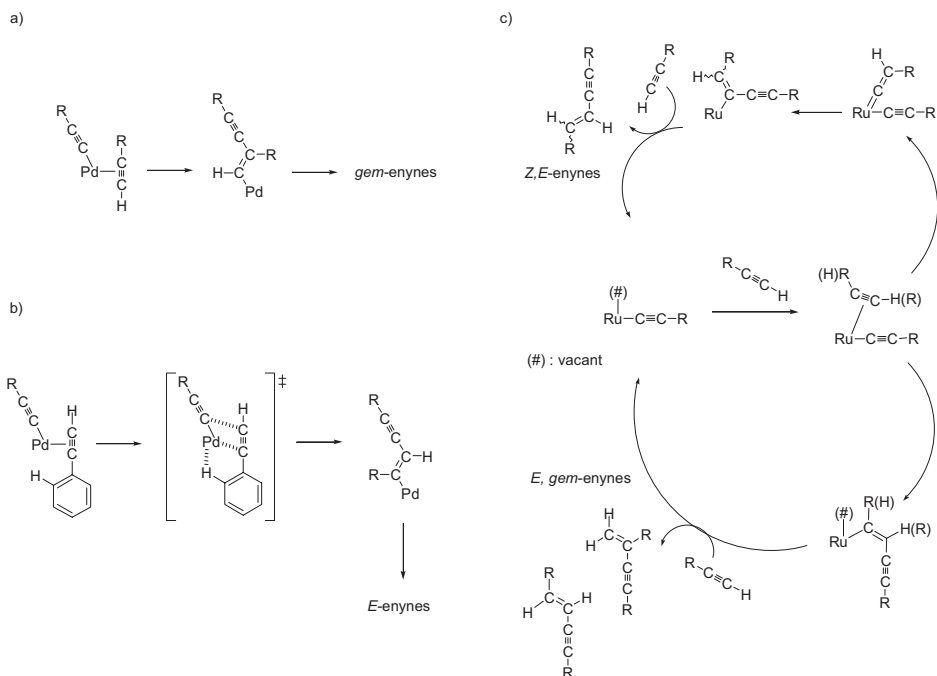
The dimerization of 1-alkynes to enynes by transition metal catalysts occurs either via alkynyl–vinylidene $\text{M}(\text{C}\equiv\text{CR})(=\text{C}=\text{CHR})$ or alkynyl–alkyne $\text{M}(\text{C}\equiv\text{CR})(\eta^2\text{-HC}\equiv\text{CR})$ coupling, by insertion into the σ Ru–C bond. Selectivity control depends on the previous orientation of the alkyne/vinylidene moiety.

In the alkyne dimerization catalyzed by *palladium systems*, all proposed mechanisms account for an alkynyl/alkyne intermediate with *cis* addition of the alkynyl C–Pd bond to the alkyne in a Markovnikov fashion, in which the palladium is placed at the less-substituted carbon, both to minimize steric hindrance and to provide the most stable C–Pd bond (Scheme 2a). The reverse regioselectivity in the palladium-catalyzed dimerization of aryl acetylenes has been attributed to an agostic interaction between the transition metal and ortho protons of the aromatic ring in the substrate (Scheme 2b) [7, 8].

For *ruthenium catalysts* a detailed study of $[(\text{PP}_3)\text{RuH}_2]$ proposes a bis(alkynyl) complex as the real catalyst. The catalytic key step involves the protonation of an alkynyl ligand by external $\text{PhC}\equiv\text{CH}$, allowing subsequent C–C bond formation between *cis* vinylidene and alkynyl groups [9].

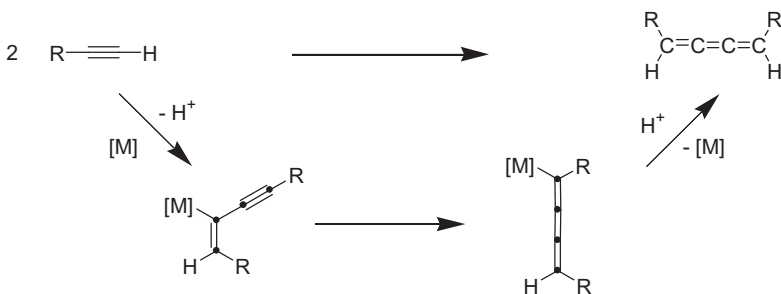
Cp^*Ru [14] and TpRu [20] complexes have also been studied in depth. As represented in Scheme 2c, the catalytic alkyne dimerization proceeds via coordinatively unsaturated ruthenium alkynyl species. Either a direct alkyne insertion and/or previous vinylidene formation are feasible pathways that determine the selectivity. The head-to-tail dimer cannot be formed by the vinylidene mechanism, whereas the *E* or *Z* stereochemistry is controlled by the nature of the alkynyl–vinylidene coupling.

It is noteworthy that alkyne dimerization may also lead to butatriene derivatives $\text{RCH}=\text{C}=\text{C}=\text{CHR}$. This product was first found for *t*-butylacetylene with



Scheme 2. Pd and Ru-catalyzed alkyne dimerization mechanisms.

[Ru(COD)(COT)]/P^tPr₃ [21], but also for benzylacetylene, and with other catalysts such as [Cp*₂RuH₃(PCy₃)]/PCy₃ [10] and [Ir(COD)Cl]₂/P^tPr₃ [16]. The [RuH₂(CO)(PPh₃)₃] precatalyst with 3-molar excess of P^tPr₃ has the best activity (90 turnover) and selectivity (96 %) for (Z)-1,4-di-*t*-butylbutatriene [21].

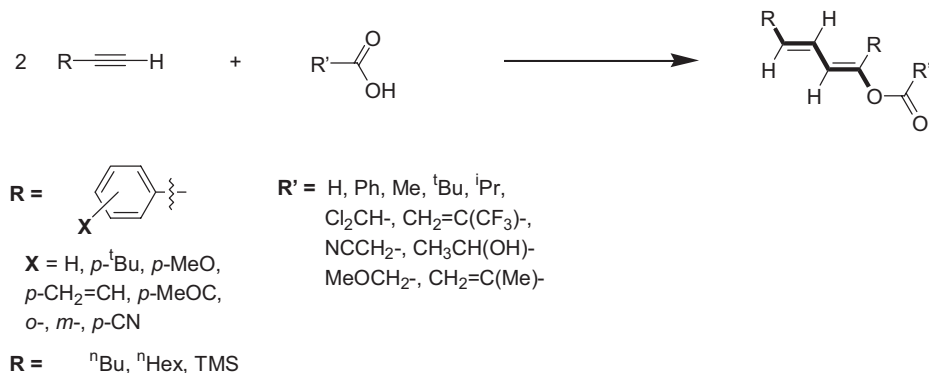


Scheme 3. Catalytic formation of the butatriene isomer.

This process is enhanced by bulky phosphines, thus butatriene formation seems to require a sterically congested environment. Otherwise the 1,3-enyne becomes the major product. Steric interaction between the phosphine ligand and the butenyne group seems to be the dominant factor promoting 1,3-metal migration to form (Z)-cumulenes (Scheme 3) [21].

1.4.1.2 Dimerization of Alkynes and Propargyl Alcohols into Functional Dienes or Cyclobutenes

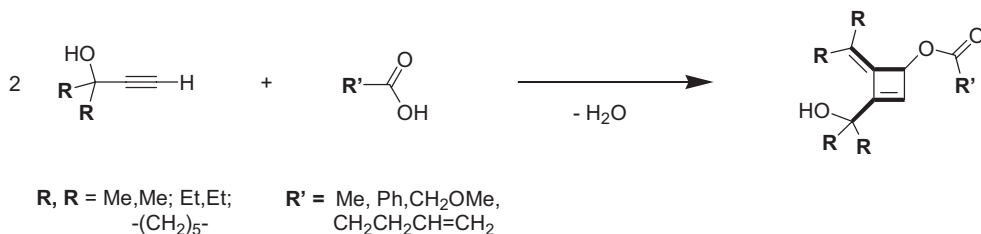
The stoichiometric head-to-head oxidative coupling of alkynes with CpRuBr(COD) affords a metallacyclic biscarbene complex [22]. This process has been used to initiate catalytic formation of the RCH=CH-CH=C(Y)R backbone, to produce *functional dienes* from alkynes by addition of H-Y . The complex $[\text{Cp}^*\text{RuCl(COD)}]$ successfully catalyzes this new chemical transformation, involving the combination of two molecules of alkynes and one molecule of carboxylic acid to afford functional conjugated dienes (Scheme 4) [23].



Scheme 4. Functional dienes from alkyne/carboxylic acid coupling.

It occurs with stereoselective formal addition of proton and carboxylate at C_1 and C_4 carbon atoms with concomitant C–C, C–H, and C–O bond formation, giving (1*E*,3*E*)-1,3-dienyl acetate as the only stereoisomer. This general reaction proceeds for a variety of alkynes and carboxylic acids and is favored by electron-withdrawing groups on arylacetylenes.

On the other hand, when propargyl alcohols are treated with the same catalyst precursor $[\text{Cp}^*\text{RuCl(COD)}]$ in the presence of a carboxylic acid, the catalytic reaction takes a different route, leading to the selective formation of alkenylenecyclobutenes (Scheme 5) [24, 25].

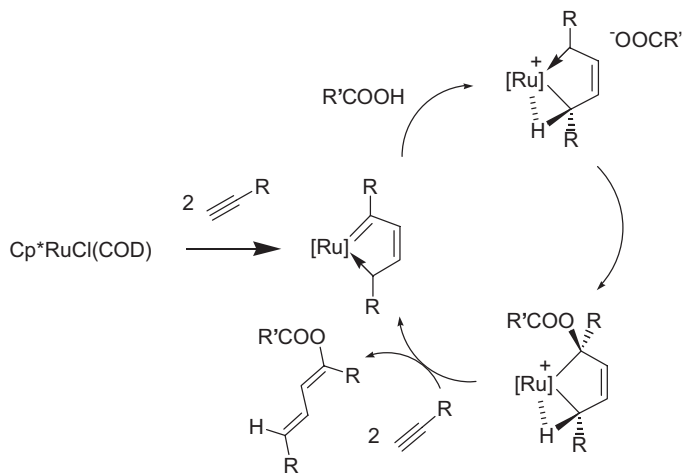


Scheme 5. Alkenylenecyclobutenes from alkynol/carboxylic acid coupling.

This novel catalytic reaction formally corresponds to an initial regioselective [2+2] head-to-head cyclodimerization of the propargyl alcohol with addition of carboxylic acid and elimination of water. Catalytic alkenyldenecyclobutene formation is general for a variety of propargyl alcohols and carboxylic acids and can also be applied to phenol derivatives.

1.4.1.2.1 Mechanism

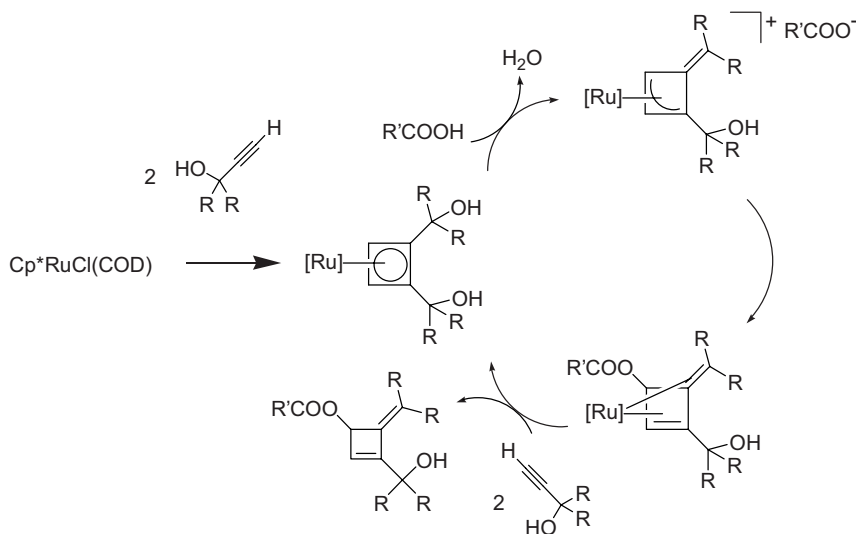
The stereoselective synthesis of 1,4-disubstituted-1,3-dienes proceeds by head-to-head oxidative coupling of two alkynes with formation of an isolable metallacyclic biscarbene ruthenium complex [23], as shown in Scheme 6. Several key experiments involving labeled reagents and stoichiometric reactions and theoretical studies support the formation of a mixed Fischer–Schrock-type biscarbene complex which undergoes protonation at one carbene carbon atom whereas the other becomes accessible to nucleophilic addition of the carboxylate anion (Scheme 6) [23].



Scheme 6. Catalytic cycle for dieny ester formation from terminal alkynes and carboxylic acid.

In the synthesis of alkylidenecyclobutenes from propargyl alcohols, stoichiometric experiments show that the first step involves [2+2] oxidative head-to-head coupling of the alkynes, leading to an isolable cyclobutadiene–ruthenium complex. Addition of acid generates a cyclobutenyl metal intermediate which undergoes carboxylate addition on the less substituted allylic carbon atom (Scheme 7).

Computational studies performed on both reactions, leading either to dieny esters or to alkylidenecyclobutenes, show that the biscarbene ruthenium intermediate requires a high activation energy to produce the cyclobutadiene complex from terminal alkynes whereas with propargyl alcohols this step occurs readily [25].

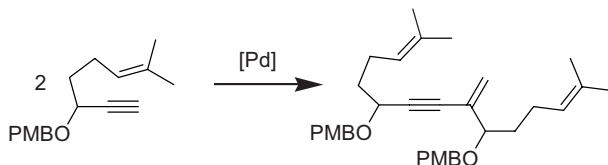


Scheme 7. Catalytic cycle for formation of alkenylidenecyclobutenes from alkynols and carboxylic acid.

1.4.1.2.2 Scope and Limitations

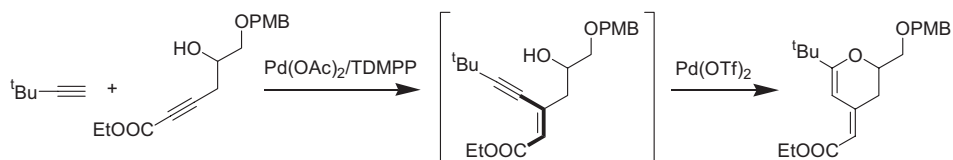
Although alkyne dimerization reactions have been observed with a variety of transition metal catalysts, selectivity is highly dependent not only on the metallic center but also on the ancillary ligands and the substrates.

Palladium catalysts have high tolerance for several functional groups irrespective of their *gem*- or *E*-selectivity [4, 6, 7]. Aldehydes, alcohols, saturated or conjugated ketones, esters, sulfones, malonates and silyl ethers have proved to be compatible. The presence of an additional double bond does not modify the coupling, enabling self-dimerization of non-conjugated enynes as depicted in Scheme 8.



Scheme 8. Catalytic dimerization of non-conjugated enynes with the Pd(OAc)₂/TDMPP system.

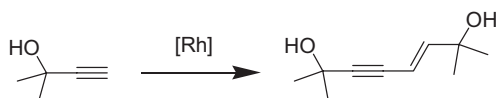
The palladium–phosphine combination has become a most useful synthetic system, because of the possibility of achieving cross-coupling reactions of terminal and activated internal alkynes. As an example, one-pot alkyne–alkynoate coupling gives dihydropyrans atom-economically and in moderate to good yield (Scheme 9) [26].



Scheme 9. Oxygen heterocycle by tandem palladium catalysis.

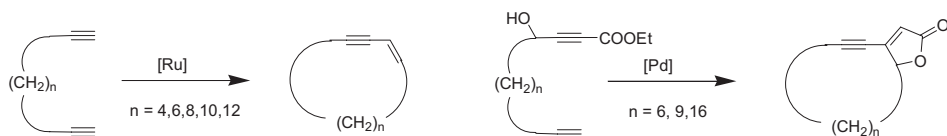
Reports on *ruthenium* catalytic activity focus more on mechanistic consideration of the prototypical phenylacetylene dimerization than in establishing its synthetic applicability. It is not unusual that changing the alkyne substituents results in reversed selectivity (i.e. $R = \text{Ph}$ or SiMe_3 gave (*E*)- or (*Z*)- isomers, respectively) [27]. Competitive alkyne cyclotrimerization ($R = \text{COOMe}$) [27] or butatriene formation ($R = \text{CH}_2\text{Ph}$, ^tBu) [10, 21] have occasionally been reported as possible drawbacks in enyne synthesis. The operating mechanism restricts the reaction to terminal alkynes.

Propargyl alcohols are also suitable substrates for dimerization, as reported early on for Wilkinson's catalyst $[\text{RhCl}(\text{PPh}_3)_3]$ [28], which provides (*E*)-head-to-head dimers as shown in Scheme 10.



Scheme 10. Head-to-head dimerization of 3-methyl-1-yn-3-ol by $[\text{RhCl}(\text{PPh}_3)_3]$ catalyst.

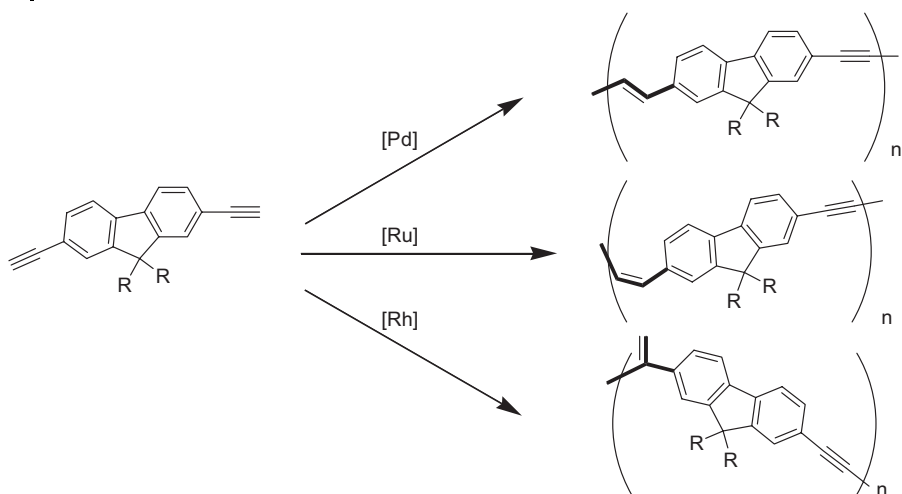
Cyclization of α,ω -diynes in moderate to high yields with high regio- and stereoselectivity has been reported with palladium [29] and binuclear ruthenium catalysts [30], to give *exo*- or *endo*-cyclic (*Z*)-1-en-3-yne, respectively (Scheme 11).



Scheme 11. *Endo*- and *exo*- cyclization of α,ω -diynes.

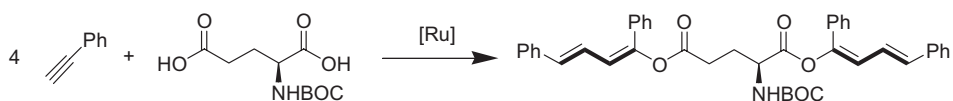
A recently developed application of this method in the field of polymers involves the synthesis of three geometrical isomers by polyaddition of diethynyl compounds, based on transition-metal-catalyzed dimerization of arylacetylenes [5]. This reaction goes highly regio- and stereoselectively and is controlled by appropriate choice of the catalyst, affording polymers with (*E*)-, (*Z*)- and *gem*-vinylene linkages with selectivity over 92 %, as illustrated in Scheme 12.

The catalytic synthesis of dienyl esters by dimerization of alkynes and addition of carboxylic acids tolerates a large variety of functional groups and carboxylic



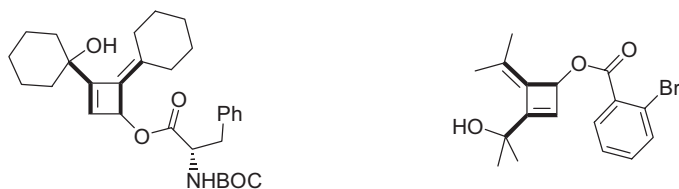
Scheme 12. Conjugated polymers with enriched (*E*)-, (*Z*)- or *gem*-vinylene linkages.

acids, and good yields (60–90 %) are obtained from combinations of several arylacetylenes and carboxylic acids. The reaction is, however, inhibited by phenols and strong acids. It can also be extended to alkylacetylenes with moderate yields of dieny l esters. Reaction of arylacetylenes with amino acids leads to dieny l amino esters when the amino group is protected. New monomers for polymerization can be obtained from dicarboxylic acids (Scheme 13) [23].



Scheme 13. Alkyne dimerization and coupling with L-glutamic acid catalyzed by $[\text{Cp}^*\text{RuCl}(\text{COD})]$.

The alkylidenecyclobutene synthesis is restricted to propargyl alcohols bearing a terminal triple bond. The scope of the reaction has been established for a variety of carboxylic acids, for example acetic, benzoic, methoxyacetic, and pent-4-enoic acid. It can also be applied to N-protected amino acids, and to phenol derivatives containing reactive $\text{sp}^2\text{-C-Br}$ bonds (Scheme 14) [24, 25].

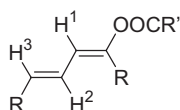


Scheme 14. Alkylidenecyclobutenes from propargyl alcohols and acids, with $[\text{Cp}^*\text{RuCl}(\text{COD})]$ as catalyst.

Experimental

Typical Procedure for Ruthenium-Catalyzed Dimerization of Terminal Alkynes with Monocarboxylic Acids [23]

To a solution of terminal alkyne (2.5 mmol, 1 equiv) in degassed dioxane (1 mL) were added $\text{Cp}^*\text{RuCl}(\text{COD})$ [31] (0.125 mmol, 5 %) and carboxylic acid (1.25 mmol, 0.5 equiv) under an inert atmosphere at room temperature. The reaction mixture was stirred at room temperature for 15 min to 45 h. The solvent was removed, and the product was purified by silica gel flash column chromatography (eluent pentane–diethyl ether mixtures) to give dimerization adduct as a white solid in 20–98 % yield. The compounds were analyzed by NMR (^1H and ^{13}C), IR, and mass spectroscopy.

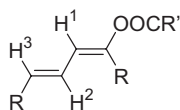


$\text{R} = \text{Ph}$, $\text{R}' = \text{Me}$

Yield: 90 %. ^1H NMR (200.131 MHz, CDCl_3) δ ppm: 2.21 (s, 3H, MeCO), 6.29 (d, $J = 11.1$ Hz, 1H, H^1), 6.67 (d, $J = 15.5$ Hz, 1H, H_3), 6.99 (dd, $J = 11.1$ Hz, $J = 15.5$ Hz, 1H, H_2), 7.21–7.53 (m, 10H, Ph). ^{13}C NMR (50.329 MHz, CDCl_3) δ ppm: 169.6, 148.4, 137.2, 134.7, 134.5, 128.9, 128.7, 128.5, 128.4, 127.8, 126.5, 123.3, 120.5, 21.1. MS (EI): m/z 264.1148 (calc for $\text{C}_{18}\text{H}_{16}\text{O}_2$ 264.1150). FTIR (KBr) ν (cm^{-1}): 3060, 3035, 3022, 1758, 1636, 1594.

Typical procedure for ruthenium-catalyzed dimerization of terminal propargylic alcohols with carboxylic acids [24, 25]

To a solution of terminal alkyne (2.5 mmol, 1 equiv) in degassed isoprene (2 mL) were added $\text{Cp}^*\text{RuCl}(\text{COD})$ [31] (0.125 mmol, 5 %) and carboxylic acid (1.25 mmol, 0.5 equiv) under an inert atmosphere at room temperature. The reaction mixture was stirred at 40 °C for 20 h. The solvent was removed and the product was purified by silica gel flash column chromatography (eluent pentane–diethyl ether mixtures) to give dimerization adduct as a viscous oil in 20–77 % yield. The compounds were analyzed by NMR (^1H and ^{13}C), IR and mass spectrometry.



$\text{R} = \text{Me}$; R' , $\text{R}'' = -(\text{CH}_2)_5-$

Yield: 66 %. ^1H NMR (200.131 MHz, CDCl_3) δ ppm: 1.4–1.75 (m, 17H, cyclohexyl + OH), 2.01 (s, 3H, MeCO), 1.96–2.08 (m, 2H, cyclohexyl CH_2), 2.37–

2.47 (m, 2H, cyclohexyl CH₂), 5.59 (d, 1H, $J=0.5$ Hz, H¹), 6.27 (s, 1H, H²). ¹³C NMR (50.329 MHz, CDCl₃) δ ppm: 171.3, 162.0, 130.7, 129.3, 127.8, 72.4, 69.4, 35.8, 35.6, 31.4, 30.8, 27.9, 27.7, 26.4, 25.5, 21.7, 21.6, 21.2. MS (EI): m/z 290.1879 (calc for C₁₈H₂₆O₃ 290.1882). FTIR (neat) ν (cm⁻¹): 3462, 2928, 1732, 1577.

1.5

anti-Markovnikov Addition to Terminal Alkynes via Ruthenium Vinylidene Intermediates

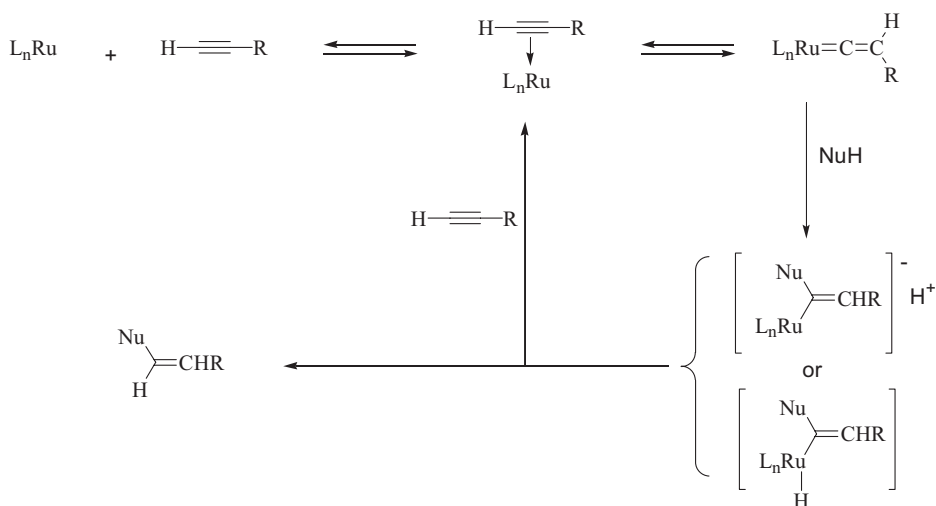
Christian Bruneau

1.5.1

Introduction

The formation of metal vinylidene complexes directly from terminal alkynes is an elegant way to perform *anti*-Markovnikov addition of nucleophiles to triple bonds [1, 2]. The electrophilic α -carbon of ruthenium vinylidene complexes reacts with nucleophiles to form ruthenium alkenyl species, which liberate this organic fragment on protonolysis (Scheme 1).

Among nucleophilic additions to catalytic metal vinylidene intermediates, tremendous effort was initially devoted to selectively perform unusual *anti*-Markovnikov addition of O-nucleophiles such as carbamates and carboxylates to terminal alkynes. The objective was to produce, in one step, useful derivatives such as



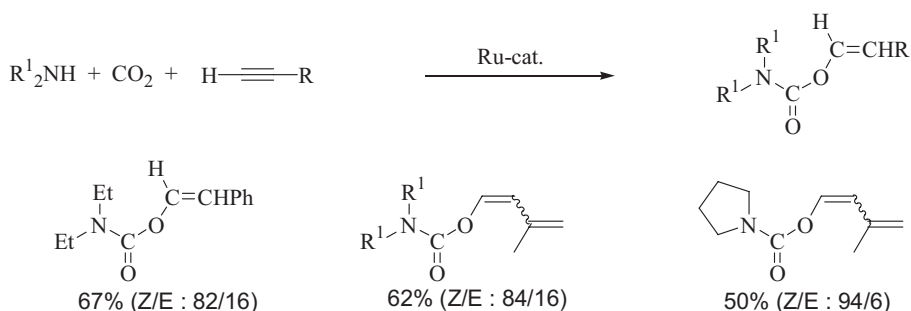
Scheme 1. General mechanism of nucleophilic addition to terminal alkynes *via* ruthenium vinylidene intermediates.

vinyllic carbamates and esters without the use of toxic reagents such as phosgene or mercury derivatives. Addition of alcohols and water to alkynes to produce enol ethers, ketones, lactones, and aldehydes are now well controlled. For these reactions, ruthenium catalysts often have excellent activity.

1.5.2

Application to the Synthesis of Vinylcarbamates

Ammonium carbamates are readily and reversibly produced on reaction of secondary amines with carbon dioxide. In the presence of a ruthenium catalyst precursors such as $\text{Ru}_3(\text{CO})_{12}$ [3], (arene) $\text{RuCl}_2(\text{PR}_3)$ [4] or $\text{Ru}(\text{methallyl})_2(\text{dppe})$ [5] (dppe = bis(diphenylphosphino)ethane) complexes, the three-component combination of a secondary amine, a terminal alkyne, and carbon dioxide selectively provides vinylcarbamates resulting from addition of carbamate to the terminal carbon of the triple bond (Scheme 2).



Scheme 2. Formation of vinylcarbamates via terminal alkyne C–H bond-activation with ruthenium catalysts.

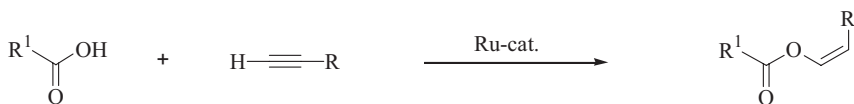
The major advantage of this one-step catalytic synthesis is that no phosgene derivative such as R^1_2NCOCl is used, which is greener than the traditional stoichiometric processes. It also enables straightforward access to vinylcarbamates, which are useful monomers for functional polymer production.

1.5.3

Application to the Synthesis of Enol Esters

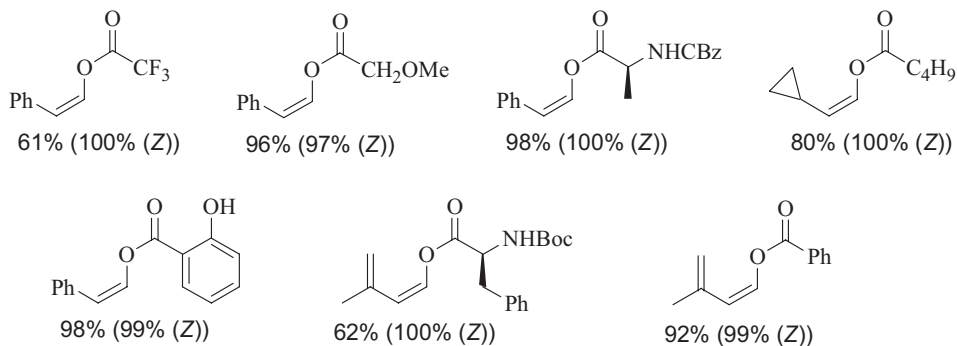
The *anti*-Markovnikov addition of carboxylic acids was attempted with the objective of producing, in one step, alkenyl esters formally produced by acylation of aldehyde enolates. Catalytic addition of carboxylic acids to terminal alkynes usually leads to Markovnikov addition products with classical ruthenium catalysts such as $\text{RuCl}_2(\text{phosphine})(\text{arene})$. Efforts were made to modify the regioselectivity of the addition by using more electron-rich catalytic ruthenium moieties. Indeed, as the vinylidene ligand is an electron-withdrawing group, tautomerization of $\text{M}(\eta^2\text{-HC}\equiv\text{CR})$ into $\text{M}(\eta^1\text{-C}=\text{CHR})$ is favored by electron-donating ancillary li-

gands bonded at the ruthenium site [6]. Success was achieved with the diphosphine ruthenium catalyst $\text{Ru}(\text{methallyl})_2(\text{diphenylphosphinobutane})$. Thus, when carboxylates are used as nucleophiles, the *anti*-Markovnikov addition of carboxylic acids to terminal alkynes occurs under mild conditions in the presence of catalytic amounts of $\text{Ru}(\text{methallyl})_2(\text{diphosphine})$, regioselectively providing (*Z*)-enol esters [7, 8].



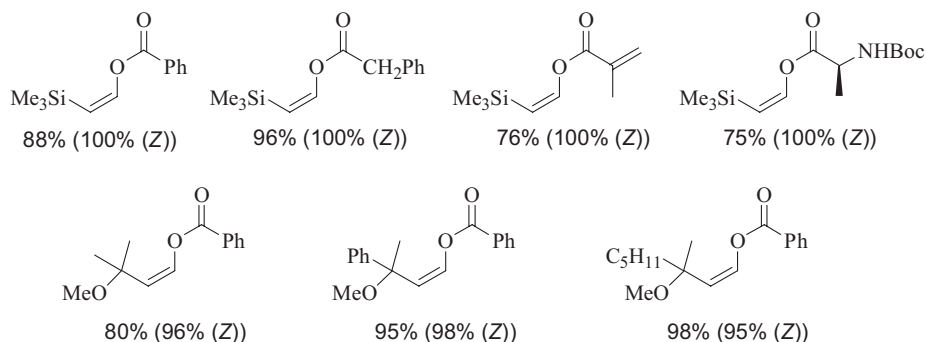
Scheme 3. Synthesis of (*Z*)-enol esters via *anti*-Markovnikov addition of carboxylic acids to terminal alkynes.

The diphosphine of choice for obtaining good regioselectivity is the bis(diphenylphosphino)butane (Scheme 4). It enables addition of a variety of carboxylic acids to phenylacetylene and hexyne. The reaction temperature, which enables complete conversion can be reduced from 80 to 0 °C when the acidity of the carboxylic acid increases in the $\text{p}K_a$ range from 5 to 1.5. The milder temperature conditions always lead to higher regioselectivity of the addition. The preparation of functionalized (*Z*)-enol esters can be conducted in apolar solvents such as toluene or pentane; dienyl esters are selectively produced from conjugated enynes [9].



Scheme 4. Preparation of enol esters and dienyl esters from terminal alkynes and carboxylic acids.

For both reactivity and regioselectivity, however, a compromise must be found between the bulkiness of the reagents (alkyne and carboxylic acid) and the steric hindrance of the diphosphine ligand, all of which are present in the coordination sphere of the ruthenium center during the catalytic process. Thus, with the more bulky trimethylsilylacetylene, the less hindered bis(diphenylphosphino)ethane ligand provides an efficient ruthenium catalyst ($\text{Ru}(\text{methallyl})_2(\text{dppe})$) for producing silylated enol esters. Better reactivity is also observed with $\text{Ru}(\text{methallyl})_2(\text{dppe})$ as catalyst precursor when propargylic ethers are used as acetylenic substrates (Scheme 5) [10].



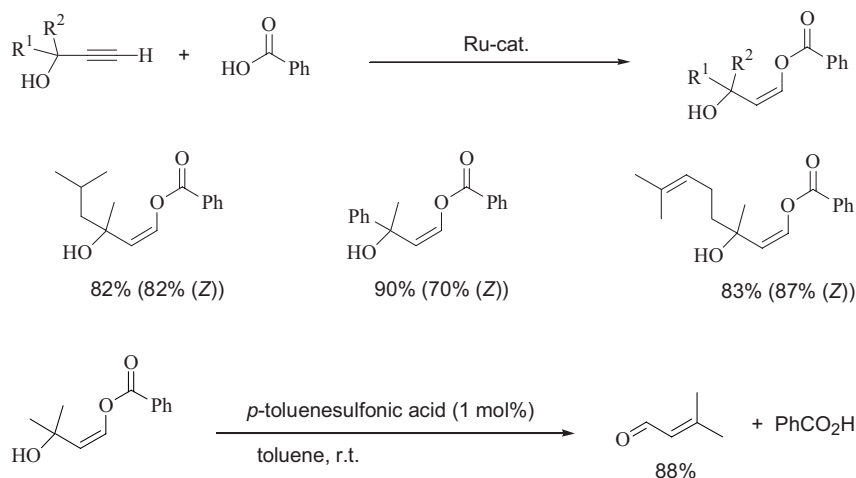
Scheme 5. Preparation of functional enol esters from trimethylsilylacetylene and propargylic ethers.

Very recently, new ruthenium catalysts, for example $\text{RuCl}_2(\text{triazol-5-ylidene})(p\text{-cymene})$ [11] and the catalytic system generated in situ from $[\text{RuCl}_2(p\text{-cymene})]_2$, tris(*p*-chlorophenyl)phosphine, and 4-dimethylaminopyridine [12], have provided efficient catalysts for synthesis of the same type of enol ester. The regio-selective cyclization of acetylenic acids containing a terminal triple bond to give unsaturated lactones was performed in the presence of catalytic amounts of $\text{Ru}(\text{tris}(\text{pyrazolyl})\text{borate})(\text{PhC}\equiv\text{C}(\text{Ph})\text{C}\equiv\text{CPh})(\text{PMe}_2\text{iPr}_2)$ [13].

1.5.4

Application to the Isomerization of Propargylic Alcohols

Propargylic alcohols are also very interesting because *anti*-Markovnikov addition of benzoic acid generates bifunctional 1,3-hydroxy esters with addition of the carboxylate to the terminal carbon of the triple bond [14, 15]. This reaction contrasts



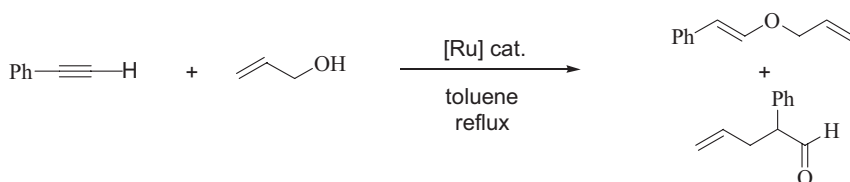
Scheme 6. Preparation of 1,3-hydroxyesters and subsequent cleavage into conjugated enals.

with the Markovnikov addition, which selectively leads to the formation of β -keto esters by intramolecular transesterification [16]. These 1,3-hydroxyesters are readily cleaved under thermal or acidic conditions to afford the conjugated enals, the formal isomerization compounds of the starting propargylic alcohols [14, 15].

1.5.5

Application to the Synthesis of Vinylic Ethers

There are not many examples of addition of alcohols to a triple bond proceeding through an *anti*-Markovnikov reaction. With $\text{RuCl}(\text{tris}(\text{pyrazolyl})\text{borate})(\text{pyridine})_2$ as catalyst, addition of allyl alcohol to phenylacetylene proceeds in 72 % overall yield in toluene under reflux, and provides a 1:1 mixture of allyl β -styryl ether and 2-phenylpent-4-enal resulting from further Claisen rearrangement (Scheme 7) [17].

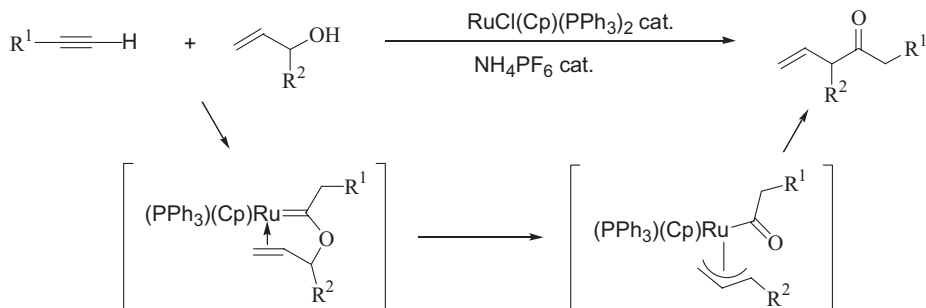


Scheme 7. Ruthenium-catalyzed addition of allyl alcohol to phenylacetylene.

1.5.6

Application to the Synthesis of Unsaturated Ketones

It is well-known that $\text{RuCl}(\text{cyclopentadienyl})(\text{PPh}_3)_2$ stoichiometrically activates terminal alkynes in the presence of a chloride abstractor to produce $[\text{Ru}(\text{cyclopentadienyl})(=\text{C}=\text{CHR})][\text{X}]$ complexes. This reaction has been used with advantage to perform *anti*-Markovnikov addition of allylic alcohols to terminal alkynes followed by intramolecular rearrangement to produce unsaturated ketones according to Scheme 8 [18, 19].

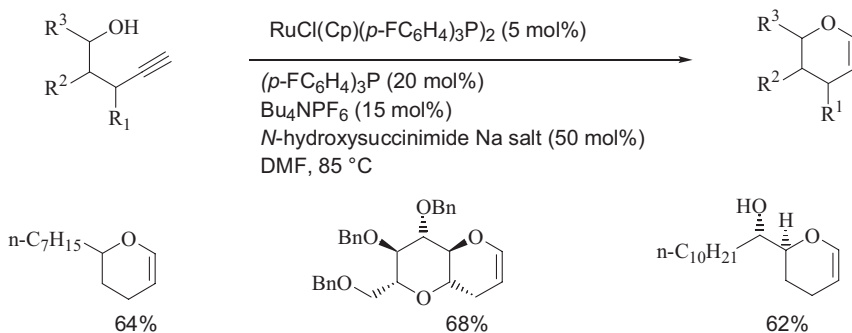


Scheme 8. Ruthenium-catalyzed addition of allyl alcohol to terminal alkynes with skeleton rearrangement.

1.5.7

Application to the Synthesis of Cyclic Enol Ethers and Lactones

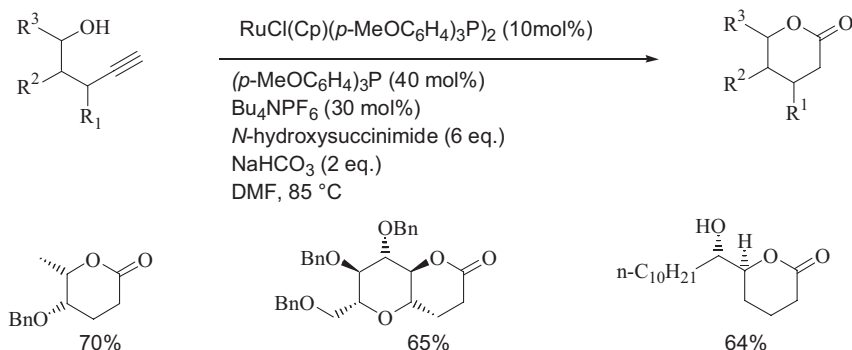
Intramolecular addition of a hydroxy group to the terminal sp-carbon of pent-4-yn-1-ols, leading to the corresponding cycloisomerization dihydropyrans, has been successfully achieved with a similar ruthenium catalyst precursor containing the electron-deficient tris(*p*-fluorophenyl)phosphine ligand, excess phosphine, and sodium *N*-hydroxysuccinimide as additives (Scheme 9) [20].



Scheme 9. Cycloisomerization of pent-4-yn-1-ols catalyzed by ruthenium catalysts bearing electron deficient phosphine ligands.

When the ruthenium precursor contains an electron-rich phosphine such as tris(*p*-methoxyphenyl)phosphine, and if a large excess of this ligand is used in the catalytic reaction, the formation of valerolactones by oxidation of a postulated transient alkoxycarbene ruthenium moiety is favored (Scheme 10) [20].

With *N*-hydroxysuccinimide as mild oxidant and RuCl(cyclopentadienyl)(cyclooctadiene) as catalyst precursor, in the presence of tris(*o*-furyl)phosphine and *n*-butylammonium bromide, a wide range of homopropargylic alcohols were transformed into five-membered γ -butyrolactones via a related cycloisomerization–oxidation reaction [21].



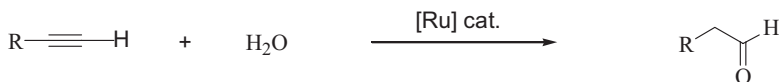
Scheme 10. Oxidative cyclization of pent-4-yn-1-ols involving ruthenium vinylidene intermediates.

It must be pointed out that tungsten [22–26] and molybdenum [26–29] carbonyl precursors also have remarkable catalytic activity in the cycloisomerization of alkynols to produce dihydropyrans and dihydrofurans via intramolecular nucleophilic addition of the hydroxy group to the terminal carbon of the triple bond, activated as a vinylidene metal species.

1.5.8

Application to the Synthesis of Aldehydes

Regioselective addition of water to triple bonds constitutes a straightforward preparation of aldehydes from terminal alkynes (Scheme 11). The *anti*-Markovnikov addition has recently been made possible by use of ruthenium catalysts such as $\text{RuCl}(\text{C}_6\text{H}_6)(\text{PPh}_2(\text{C}_6\text{F}_5)) + 3 \text{PPh}_2(\text{C}_6\text{F}_5)$ [30], $[\text{RuCl}_2(\text{C}_6\text{H}_6)]_2$ in the presence of an excess of the water-soluble ligand $\text{P}(3\text{-C}_6\text{H}_5\text{SO}_3\text{Na})_3$ [30], $\text{RuCl}(\text{Cp})(\text{phosphine})_2$ [31], $\text{RuCl}(\text{Cp})(\text{diphosphine})$ [31], $\text{RuCl}(\text{indenyl})(\text{phosphine})_2$ [32], and $[\text{Ru}(\text{Cp})(\text{H}_2\text{O})(2\text{-imidazolylphosphine})_2][\text{CF}_3\text{SO}_3]$ [33]. Reaction of water with terminal propargylic alcohols has also been used to prepare hydroxy aldehydes by *anti*-Markovnikov addition in the presence of $\text{RuCl}(\text{indenyl})(\text{PPh}_3)_2$ in an isopropanol–water mixture, or in water containing a surfactant as solvent [32]. It is noteworthy that in the presence of $\text{RuCl}(\text{Cp})(\text{PMe}_3)_2$ as catalyst precursor, the *anti*-Markovnikov addition is accompanied by a dehydration reaction and conjugated enals are obtained [34].



Scheme 11. Preparation of aldehydes from terminal alkynes and water in the presence of ruthenium catalyst.

1.5.9

Scope and Limitations

These reactions illustrate the importance of ruthenium vinylidene species, as activated forms of terminal alkynes, in catalysis, because they favor the addition of *O*-nucleophiles (carbamic and carboxylic acids, alcohols, water) to terminal alkynes and completely reverse the expected regioselectivity of the addition. These examples also show that the activation processes are very sensitive to the nature of the nucleophiles, and the success of the *anti*-Markovnikov addition to terminal alkynes is highly dependent on both the electron richness and steric hindrance of the ancillary ligands coordinated to the active site.

Experimental

Synthesis of Vinylcarbamates – Typical Experiment –

(Z)- β -[[(Diethylcarbamoyl)oxy]styrene [4]

Diethylamine (20 mmol), phenylacetylene (10 mmol), and $\text{RuCl}_2(\text{C}_6\text{Me}_6)(\text{PMe}_3)$ (0.2 mmol) in 10 mL acetonitrile were placed in a 125-mL stainless steel autoclave. Carbon dioxide was used first to flush out the reactor and then to pressurize it to a starting pressure of 5 MPa. The reaction mixture was stirred at 125 °C for 20 h. After elimination of the solvent under reduced pressure, the product was purified by flash chromatography (1:1 CH_2Cl_2 –petroleum ether) and isolated in 67 % yield. ^1H NMR (C_6D_6 , 300 MHz): δ = 0.84 (t, 3H, J = 7.0 Hz, Me), 0.90 (t, 3H, J = 7.0 Hz, Me), 2.95 (q, 2H, J = 7.0 Hz, NCH_2), 3.06 (q, 2H, J = 7.0 Hz, NCH_2), 6.27 (d, 1H, J = 12.9 Hz, =CHPh), 7.40 (m, 5H, Ph), 8.16 (d, 1H, J = 12.9 Hz, =CHO).

Preparation of the Catalyst

$[\text{RuCl}_2(\text{C}_6\text{Me}_6)]_2$ is prepared by heating a finely powdered mixture of 10.0 g (16.3 mmol) commercially available $[\text{RuCl}_2(p\text{-cymene})]_2$ and 30 g (185 mmol) hexamethylbenzene at 205 °C for 20 h. After cooling, the reaction mixture is stirred in hot toluene for 1 h and the remaining solid is isolated by filtration of the hot solution. After washing with toluene and diethyl ether, $[\text{RuCl}_2(\text{C}_6\text{Me}_6)]_2$ is obtained as an orange powder in 96 % yield. Trimethylphosphine (6 mmol, 0.7 mL) is then added to a dichloromethane solution (40 mL) containing 2 g (3 mmol) $[\text{RuCl}_2(\text{C}_6\text{Me}_6)]_2$ under an inert atmosphere and the solution is stirred for 4 h. The resulting solution is evaporated under vacuum and the residue is extracted with boiling ethanol. The hot solution is filtered and dark-red crystals of $\text{RuCl}_2(\text{C}_6\text{Me}_6)(\text{PMe}_3)$ precipitate when the solution is cooled (90 %). ^1H NMR (CDCl_3 , 200 MHz) δ = 1.43 (d, 9H, J_{PH} = 10.5 Hz, PMe_3), 2.00 (d, 18H, J_{PH} = 0.7 Hz C_6Me_6). $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 81 MHz) δ = 1.96.

Synthesis of Enol Esters – Typical Experiment – (Z)-3-Methylbuta-1,3-dien-1-yl benzoate [9]

A solution of 1.22 g (10 mmol) benzoic acid, 0.86 g (11 mmol) isopropenylacetylene and 64 mg (0.1 mmol) $\text{Ru}(\text{methallyl})_2(\text{diphenylphosphinobutane})$ in 5 mL toluene was stirred at 50 °C for 18 h. The product was purified by silica-gel chromatography and isolated in 92 % yield. ^1H NMR (CDCl_3 , 300 MHz): δ = 2.18 (t, 3H, J = 1.1 Hz, Me), 4.98 and 5.11 (m, 2H, CH_2), 5.47 (dd, 1H, J = 7.3 Hz, 0.7 Hz, =CH), 7.22 (d, 1H, J = 7.3 Hz, =CHO), 7.45–8.10 (m, 5H, Ph).

Preparation of the Catalyst

$\text{Ru}(\text{methallyl})_2(\text{cyclooctadiene})$ is prepared by addition of polymeric dichloro(cyclooctadiene)ruthenium to a suspension of (2-methylpropenyl)magnesium chloride in diethyl ether, and stirring at room temperature for 1.5 h. After hydrolysis with cold water at –40 °C, the reaction mixture is extracted twice with diethyl ether. Evaporation of the solvent furnishes a gray powder in 80 % yield. This complex (2.0 g, 6.26 mmol) and 2.6 g (6.10 mmol) 1,3-bis(diphenylphosphino)butane are

then heated under reflux for 5 h in 70 mL hexane under argon. After cooling, a yellow powder is isolated by filtration, washed three times with 10 mL hexane and dried in vacuo to give 3.07 g (79 %) Ru(methallyl)₂(diphenylphosphinobutane). ¹H NMR (CD₂Cl₂, 300 MHz): δ = 0.56 (dd, 2H, *J* = 15.9, 4.9 Hz, allylic CH₂), 1.02 (d, 2H, *J* = 13.9 Hz, allylic CH₂), 1.05 (s, 2H, allylic CH₂), 1.60 (m, 2H, P(CH₂)₄P), 1.84 (s, 6H, Me), 2.00 (m, 2H, P(CH₂)₄P), 2.12 (m, 2H, allylic CH₂), 2.20–2.40 (m, 2H, P(CH₂)₄P), 2.70–2.90 (m, 2H, P(CH₂)₄P), 7.00–7.70 (m, 20H, Ph). ³¹P{¹H} NMR (CD₂Cl₂, 121 MHz): δ = 44.58.

References to Chapter 1 – C–H Transformation at Terminal Alkynes

References to Section 1.1

- 1 *Modern Acetylene Chemistry* (Eds.: Stang, P. J.; Diederich, F.), VCH, Weinheim, 1995.
- 2 Simandi, L. I. in *The Chemistry of Functional Groups, Supplement C, pt 1* (Eds.: Patai, S.; Rappoport, Z.), Wiley, New York, 1983, pp. 529–534.
- 3 (a) Wakefield, B. J. *Organomagnesium Methods in Organic Synthesis*, Academic Press, London, 1995, Ch. 3, pp. 46–48; (b) Brandsma, L. *Preparative Acetylene Chemistry*, 2nd edn, Elsevier, Amsterdam, 1988; (c) Wakefield, B. J. *Organolithium Methods*, Academic Press, London, 1988, Ch. 3, p. 32.
- 4 (a) Keim, R. *Organosilver Compounds*, Gmelin Handbuch der Anorganischen Chemie, 8th edn, Berlin, 1975; (b) Breitinger, D. K.; Herrmann, W. A. *Synthetic Methods of Organometallic and Inorganic Chemistry*, Vol. 5, Copper, Silver, Gold, Zinc, Cadmium, and Mercury, Herrmann, W. A. (Ed.), Thieme, New York, 1999; (c) Krause, N. *Modern Organocopper Chemistry*, Wiley–VCH: Weinheim, 2002.
- 5 (a) Favorski, A. E.; Skossarewsky, M. *Russ. J. Phys. Chem. Soc.* **1900**, 32, 652; (b) Favorski, A. E.; Skossarewsky, M. *Bull. Soc. Chim.* **1901**, 26, 284.
- 6 (a) Tedeschi, R. J.; Kindley, L. M.; Huckel R. W.; Russell, J. P.; Casey, A. W.; Clark, G. S. *J. Org. Chem.* **1963**, 28, 1740; (b) Tedeshi, R. J. *J. Org. Chem.* **1965**, 30, 3045.
- 7 Babler, J. H.; Liptak, V. P.; Phan, N. *J. Org. Chem.* **1996**, 61, 416.
- 8 Busch-Petersen, J.; Bo, Y. X.; Corey, E. J. *Tetrahedron Lett.* **1999**, 40, 2065.
- 9 Tzalis, D.; Knochel, P. *Angew. Chem. Int. Ed.* **1999**, 38, 1463.
- 10 Pu, L. *Tetrahedron* **2003**, 59, 9873 and references therein.
- 11 (a) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **1999**, 121, 11245; (b) Frantz, D. E.; Fässler, R.; Tomooka, C. S.; Carreira, E. M. *Acc. Chem. Res.* **2000**, 33, 373.
- 12 Fässler, R.; Tomooka, C. S.; Frantz, D. E.; Carreira, E. M. *Proceedings of the National Academy of Sciences* **2004**, 101, 5843.
- 13 Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, 122, 1806.
- 14 Jiang, B.; Si, Y. G. *Tetrahedron Lett.* **2002**, 43, 8323.
- 15 Sasaki, H.; Boyall, D.; Carreira, E. M. *Helv. Chim. Acta* **2001**, 84, 964.
- 16 Boyall, D.; Lopez, F.; Sasaki, H.; Frantz, D.; Carreira, E. M. *Org. Lett.* **2000**, 2, 4233.
- 17 (a) Jiang, B.; Chen, Z. L.; Xiong, W. N. *Chem. Commun.* **2002**, 1524; (b) Jiang B, Si Y. G. *Adv. Synth. Catal.* **2004**, 346, 669.
- 18 Jiang, B; Chen, Z.; Tang, X. *Org. Lett.* **2002**, 4, 3451.
- 19 Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, 123, 9687.
- 20 (a) Trost, B. M.; Ball, Z. T.; Jøge, T. *Angew. Chem. Int. Ed.* **2003**, 42, 3415; (b) El-Sayed, E.; Anand, N. K.; Carreira, E. M. *Org. Lett.* **2001**, 3, 3017.
- 21 (a) Amador, M.; Ariza, X.; Garcia, J.; Ortiz, J. *Tetrahedron Lett.* **2002**, 43, 2691; (b) Diez, R. S.; Adger, B.; Carreira, E. M. *Tetrahedron* **2002**, 58, 8341.

- 22 Trost, B. M.; Ameriks, M. K. *Org. Lett.* **2004**, 6, 1745.
- 23 McDonald, F. E.; Davidson, M. H. *Org. Lett.* **2004**, 6, 1601.
- 24 (a) Maezaki, N.; Tominaga, H.; Kojima, N.; Yanai, M.; Urabe, D.; Tanaka, T. *Chem. Commun.* **2004**, 4, 406; (b) Kojima, N.; Maezaki, N.; Tominaga, H.; Yanai, M.; Urabe, D.; Tanaka, T. *Chem. Eur. J.* **2004**, 10, 672; (c) Maezaki, N.; Kojima, N.; Tominaga, H.; Yanai, M.; Tanaka, T. *Org. Lett.* **2003**, 5, 1411; (d) Maezaki, N.; Kojima, N.; Asai, M.; Tominaga, H.; Tanaka, T. *Org. Lett.* **2002**, 4, 2977.
- 25 Rozner, E.; Xu, Q. *Org. Lett.* **2003**, 5, 3999.
- 26 Smith, A. B., III; Dae-Shik, K. *Org. Lett.* **2004**, 6, 1493.
- 27 Amador, M.; Ariza, X.; Garcia, J.; Ortiz, J. *Tetrahedron Lett.* **2002**, 43, 2691.
- 28 Murga, J.; Garcia-Fortanet, J.; Carda, M.; Marco, J. A. *Tetrahedron Lett.* **2003**, 44, 1737.
- 29 (a) Bode, J. W.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, 123, 3611; (b) Bode, J. W.; Carreira, E. M. *J. Org. Chem.* **2001**, 66, 6410.
- 30 (a) Fettes, A.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2002**, 41, 4098; (b) Fettes, A.; Carreira, E. M. *J. Org. Chem.* **2003**, 68, 9274.
- 31 Reber, S.; Knöpfel, T. F.; Carreira, E. M. *Tetrahedron* **2003**, 59, 6813.
- (b) K. Sonogashira, p. 493–549, in *Handbook of Organopalladium Chemistry for Organic Synthesis*, (E. Negishi, A. deMeijere, eds.), Wiley–Interscience, New York **2002**.
- 7 R. R. Tykwinski, *Angew. Chem. Int. Ed.* **2003**, 42, 1566–1568.
- 8 *Modern Acetylene Chemistry*, P. J. Stang, F. Diederich (Eds.), VCH, Weinheim, **1995**.
- 9 W. A. Herrmann, V. P. W. Böhm, C.-P. Reisinger, *J. Organomet. Chem.* **1999**, 576, 23–41.
- 10 C. Amatore, S. Bensalem, S. Ghalem, A. Jutand, Y. Medjour, *Eur. J. Org. Chem.* **2004**, 366–371.
- 11 The role of copper acetylide is well established, while it is not clear whether copper also acts as a scavenger for phosphines.
- 12 K. Sonogashira, T. Yatake, Y. Tohda, S. Takahashi, N. Hagihara, *Chem. Commun.* **1977**, 291–292.
- 13 V. Grossshenny, F. M. Romero, R. Ziessel, *J. Org. Chem.* **1997**, 62, 1491–1500.
- 14 J. P. Stambuli, M. Bühl, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, 124, 9346–9347.
- 15 M. G. Andreu, A. Zapf, M. Beller, *Chem. Commun.* **2001**, 2745–2746.
- 16 A. F. Littke, G. C. Fu, *Angew. Chem. Int. Ed.* **2002**, 41, 4176–4211.
- 17 P. Fitton, E. A. Rick, *J. Organomet. Chem.* **1971**, 28, 287–291.
- 18 F. Liu, E. Negishi, *J. Org. Chem.* **1997**, 62, 8591–8594.
- 19 H. Plenio, J. Hermann, A. Sehring, *Chem. Eur. J.* **2000**, 6, 1820–1826.
- 20 (a) N. G. Kundu, M. W. Khan, *Tetrahedron* **2000**, 56, 4777–4783; (b) G. W. Kabalka, L. Wang, R. M. Pagni, *Tetrahedron* **2001**, 57, 8017–8022.
- 21 S. Höger, *Chem. Eur. J.* **2004**, 10, 1321–1329.
- 22 R. Diercks, K. P. C. Vollhardt, *J. Am. Chem. Soc.* **1986**, 108, 3150–3151.
- 23 J. M. Tour, *Acc. Chem. Res.* **2000**, 33, 791–804.
- 24 S. H. Chanteau, J. M. Tour, *Tetrahedron Lett.* **2001**, 42, 3057–3060.
- 25 V. J. Pugh, Q.-S. Hu, X. Zuo, F. D. Lewis, L. Pu, *J. Org. Chem.* **2001**, 66, 6136–6140.

References and Notes to Section 1.2

- 1 R. D. Stephens, C. E. Castro, *J. Org. Chem.* **1963**, 28, 3313–3315.
- 2 K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, 4467–4470.
- 3 The name of Sonogashira (or Sonogashira–Hagihara) is commonly employed to identify this reaction, while even for the copper-free procedures Heck and Cassar are rarely mentioned.
- 4 H. A. Dieck, R. F. Heck, *J. Organomet. Chem.* **1975**, 93, 259–263.
- 5 L. Cassar, *J. Organomet. Chem.* **1975**, 93, 253–257.
- 6 Recent reviews on Pd-catalyzed alkynylation: (a) E. Negishi, L. Anastasia, *Chem. Rev.* **2003**, 103, 1979–2017;

- 26 J. B. Arterburn, K. Venkateswara, R. Perry, M. C. Perry, *Tetrahedron Lett.* **2000**, 41, 839–842.
- 27 K. C. Nicolaou, W.-M. Dai, *Angew. Chem. Int. Ed. Engl.* **1991**, 30, 1387–1416.
- 28 M. Inouye, K. Takahashi, H. Nakazumi, *J. Am. Chem. Soc.* **1999**, 121, 341–345.
- 29 J. Wu, M. D. Watson, L. Zhang, Z. Wang, K. Müllen, *J. Am. Chem. Soc.* **2004**, 126, 177–186.
- 30 J. N. Wilson, S. M. Waybright, K. McAlpine, U. H. F. Bunz, *Macromolecules* **2002**, 35, 3799–3800.
- 31 P. Nussbaumer, WO 9628430, **1996**.
- 32 K. Königsberger, G.-P. Chen, R. R. Wu, M. J. Girgis, K. Prasad, O. Repic, T. J. Blacklock, *Org. Proc. Res. Dev.* **2003**, 7, 733–742.
- 33 U. Beutler, J. Mazacek, G. Penn, B. Schenkel, D. Wasmuth, *Chimica* **1996**, 50, 154–156.
- 34 C. Y. Chen, D. R. Liebermann, R. D. Larsen, R. A. Reamer, T. R. Verhoeven, P. J. Reider, J. F. Cottrell, P. G. Houghton, *Tetrahedron Lett.* **1994**, 35, 6981–6983.
- 35 G. W. Parshall, W. A. Nugent, *Chemtech* **1988**, 376–378.
- 36 *Classics in Total Synthesis*, K. C. Nicolaou, E. J. Sorensen (eds.), Wiley–VCH, Weinheim, **1996**.
- 37 *Chemistry and Biology of Naturally-Occurring Acetylenes and Related Compounds*, J. Lam, H. Breteler, T. Arnason, L. Hansen (eds.), Elsevier, Amsterdam, **1988**.
- 38 R. Singh, G. Just, *J. Org. Chem.* **1989**, 54, 4453–4457.
- 39 K. Hirota, Y. Kitade, Y. Isobe, Y. Maki, *Heterocycles* **1987**, 26, 355–358.
- 40 K. Sonogashira in *Comprehensive Organic Synthesis* B. M. Trost, I. Fleming (Eds.), Pergamon Press, Oxford, p. 521–548, Vol. 3, **1991**.
- 41 S. Thorand, N. Krause, *J. Org. Chem.* **1998**, 63, 8551.
- 42 T. Hundertmark, A. F. Littke, S. L. Buchwald, G. C. Fu, *Org. Lett.* **2000**, 2, 1729–1731.
- 43 V. P. W. Böhm, W. A. Herrmann, *Eur. J. Org. Chem.* **2000**, 3679–3681.
- 44 M. Ansorge, T. J. J. Müller, *J. Organomet. Chem.* **1999**, 585, 174–178.
- 45 M. R. Buchmeiser, T. Schareine, R. Kempe, K. Wurst, *J. Organomet. Chem.* **2001**, 634, 39–46.
- 46 M. R. Eberhard, Z. Wang, C. M. Jensen, *Chem. Commun.* **2002**, 818–819.
- 47 A. Köllhofer, T. Pullmann, H. Plenio, *Angew. Chem. Int. Ed.* **2003**, 42, 1056–1058.
- 48 D. Gelman, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2003**, 115, 6175–6178.
- 49 Z. Xu, J. S. Moore, *Angew. Chem., Int. Ed. Engl.* **1993**, 32, 246–248.
- 50 A. S. Hay, *J. Org. Chem.* **1960**, 25, 1275–1276.
- 51 D. Méry, K. Heuzé, D. Astruc, *Chem. Commun.* **2003**, 1934–1935.
- 52 X. Fu, S. Zhang, J. Yin, D. Schumacher, *Tetrahedron Lett.* **2002**, 43, 6673–6676.
- 53 D. A. Alonso, C. Nájera, M. C. Pacheco, *Tetrahedron Lett.* **2002**, 43, 9365–9368.
- 54 A. C. Hillier, G. A. Grasa, M. S. Viciu, H. M. Lee, C. Yang, S. P. Nolan, *J. Organomet. Chem.* **2002**, 653, 69–82.
- 55 M. J. Mio, L. C. Kopel, J. B. Braun, T. L. Gadzikwa, K. L. Hull, R. G. Brisbois, R. A. Batey, M. Shen, A. J. Lough, *Org. Lett.* **2002**, 4, 1411–1414.
- 56 Y. Ma, C. Song, W. Jiang, Q. Wu, Y. Wang, X. Liu, M. B. Andrus, *Org. Lett.* **2003**, 5, 3317–3319.
- 57 W. A. Herrmann, C.-P. Reisinger, M. Spiegler, *J. Organomet. Chem.* **1998**, 557, 93–96.
- 58 C. Yang, S. P. Nolan, *Organometallics* **2002**, 21, 1020.
- 59 D. Gelman, D. Tselikhovsky, G. A. Molander, J. Blum, *J. Org. Chem.* **2002**, 67, 6287–6290.
- 60 A. Fürstner, G. Seidel, *Tetrahedron* **1995**, 51, 11165–11176.
- 61 J. A. Soderquist, K. Matos, A. Rane, J. Ramos, *Tetrahedron Lett.* **1995**, 36, 2401–2402.
- 62 G. A. Molander, B. W. Katona, F. Machrouhi, *J. Org. Chem.* **2002**, 67, 8416–8423.
- 63 L. Anastasia, E. Negishi, *Org. Lett.* **2001**, 3, 3111–3113.
- 64 E. Negishi, M. Qian, F. Zeng, L. Anastasia, D. Babinski, *Org. Lett.* **2003**, 5, 1597–1600.
- 65 L. Wang, P. Li and Y. Zhang, *Chem. Commun.* **2004**, 514–515.

- 66 A. Soheili, J. Albaneze-Walker, J. A. Murry, P. G. Dormer, D. L. Hughes, *Org. Lett.* **2003**, 5, 4191–4194.
- 67 M. Erdélyi, A. Gogoll, *J. Org. Chem.* **2001**, 66, 4165–4169.
- 68 N. E. Leadbeater, M. Marco, B. J. Tominack, *Org. Lett.* **2003**, 5, 3919–3922.
- 69 *Thematic Issue: Recoverable Catalysts and Reagents*, J. A. Gladysz (ed.), *Chem. Rev.* **2002**, 102.
- 70 C. C. Tzschucke, C. Markert, W. Bannwarth, S. Roller, A. Hebel, R. Haag, *Angew. Chem. Int. Ed.* **2002**, 41, 3964–4000.
- 71 D. E. Bergbreiter, *Chem. Rev.* **2002**, 102, 3345–3384.
- 72 H. Remmele, A. Köllhofer, H. Plenio, *Organometallics* **2003**, 22, 4098–4103.
- 73 A. Datta, K. Ebert, H. Plenio, *Organometallics* **2003**, 22, 4685–4691.
- 74 J. Hillerich, H. Plenio, *Chem. Commun.* **2003**, 3024–3025.
- 75 *Aqueous-Phase Organometallic Chemistry*, B. Cornils, W. A. Herrmann (eds.), Wiley–VCH, Weinheim, **1998**.
- 76 D. E. Bergbreiter, P. L. Osburn, A. Wilson, E. M. Sink, *J. Am. Chem. Soc.* **2000**, 122, 9058–9064.
- 77 A. Köllhofer, H. Plenio, *Chem. Eur. J.* **2003**, 9, 1416–1425.
- 78 A. Datta, H. Plenio, *Chem. Commun.* **2003**, 1504–1505.
- 79 T. Fukuyama, M. Shinmen, S. Nishitani, M. Sato, I. Ryu, *Org. Lett.* **2002**, 4, 1691–1694.
- 80 C. Markert, W. Bannwarth, *Helv. Chim. Acta*, **2002**, 85, 1877–1882.
- 81 E. Gonthier, R. Breinbauer, *Synlett.* **2003**, 1049–1051.
- 82 Y. Liao, R. Futhi, M. Reitman, Y. Zhang, *Tetrahedron Lett.* **2001**, 42, 1815–1818.
- 83 B. M. Choudary, S. Madhi, N. S. Chowdari, M. L. Kantam, B. Sreedhar, *J. Am. Chem. Soc.* **2002**, 124, 14127–14136.
- 84 B. M. Choudary, S. Madhi, M. L. Kantam, B. Sreedhar, Y. Iwasawa, *J. Am. Chem. Soc.* **2004**, 126, 2292–2293.
- 85 M. Moreno-Manas, R. Pleixats, *Acc. Chem. Res.* **2003**, 36, 638–643.

References and Notes to Section 1.3

- 1 C. Glaser, *Ber. Dtsch. Chem. Ges.* **1869**, 2, 422–424; C. Glaser, *Ann. Chem. Pharm.* **1870**, 154, 137–171.
- 2 P. Siemsen, R. C. Livingston, F. Diederich, *Angew. Chem.* **2000**, 112, 2740–2767; *Angew. Chem., Int. Ed.* **2000**, 39, 2632–2657.
- 3 W. Chodkiewicz, P. Cadiot, C. R. Hebd. *Seances Acad. Sci.* **1955**, 241, 1055–1057; W. Chodkiewicz, *Ann. Chim. (Paris)* **1957**, 2, 819–869.
- 4 A. S. Hay, *J. Org. Chem.* **1962**, 27, 3320–3321.
- 5 P. Siemsen, U. Gubler, C. Bosshard, P. Günter, F. Diederich, *Chem. Eur. J.* **2001**, 7, 1333–1341.
- 6 S. Kammermeier, R. R. Tykwinsky, P. Siemsen, P. Seiler, F. Diederich, *Chem. Comm.* **1998**, 1285–1286.
- 7 (a) G. Eglinton, A. R. Galbraith, *Chem. Ind. (London)* **1956**, 737–738; (b) G. Eglinton, A. R. Galbraith, *J. Chem. Soc.* **1959**, 889–896.
- 8 F. Sondheimer, *Pure Appl. Chem.* **1963**, 7, 363–388.
- 9 A. P. H. J. Schenning, J.-D. Arndt, M. Ito, A. Stoddard, M. Schreiber, P. Siemsen, R. E. Martin, C. Boudon, J.-P. Gisselbrecht, M. Gross, V. Gramlich, F. Diederich, *Helv. Chim. Acta* **2001**, 84, 296–334.
- 10 (a) L. G. Fedenok, V. M. Berdnikov, M. S. Shvartsberg, *J. Org. Chem. USSR* **1973**, 9, 1806–1809; (b) L. G. Fedenok, V. M. Berdnikov, M. S. Shvartsberg, *J. Org. Chem. USSR* **1976**, 12, 1385–1387; (c) L. G. Fedenok, V. M. Berdnikov, M. S. Shvartsberg, *J. Org. Chem. USSR* **1978**, 14, 1328–1333; (d) L. G. Fedenok, V. M. Berdnikov, M. S. Shvartsberg, *J. Org. Chem. USSR* **1978**, 14, 1334–1337; (e) H. M. Hoan, S. M. Brailovskii, O. N. Temkin, *Kinet. Catal. (Engl. Transl.)* **1994**, 35, 242–246; (f) F. Bohlmann, H. Schönowsky, E. Inhoffen, G. Grau, *Chem. Ber.* **1964**, 97, 794–800; (g) B. M. Mykhalichko, *Russ. J. Coord. Chem. (Engl. Transl.)* **1999**, 25, 336–341.

- 11 (a) P. Cadiot, W. Chodkiewicz in *Chemistry of Acetylenes* (Ed.: H. G. Viehe), Dekker, New York, **1969**, chap. 9, pp. 597–647; (b) H. G. Viehe, *Chem. Ber.* **1959**, 92, 3064–3075.
- 12 For detailed description of syntheses, isolations and characterizations, see: P. Siemsen, ETH Dissertation 13788, Zürich **2000**, pp. 96–138.
- 13 L. Brandsma, *Preparative Acetylenic Chemistry*, Elsevier, Amsterdam, **1988**, chap. 10, pp. 219–227.
- 16 T. Ohmura, S. Yorozya, Y. Yamamoto, N. Miyaura, *Organometallics* **2000**, 19, 365–367.
- 17 Heeres, H. J.; Teuben, J. H. *Organometallics* **1991**, 10, 1980–1986.
- 18 den Haan, K. H.; Wielstra, Y.; Teuben, J. H. *Organometallics* **1987**, 6, 2053–2060.
- 19 A. K. Dash, I. Gourevich, J. Q. Wang, J. Wang, M. Kapon, M. S. Eisen *Organometallics* **2001**, 20, 5084–5104.
- 20 S. Pavlik, C. Gemel, C. Slugovc, K. Mereiter, R. Schmid, K. Kirchner, *J. Organomet. Chem.* **2001**, 617–618, 301–310.

References and Notes to Section 1.4

- 1 K. C. Nicolaou, W. M. Dai, S.C. Tsay, V. A. Estevez, W. Wrasidlo, *Science* **1992**, 256, 1172–1178.
- 2 B. M. Trost, *Angew. Chem., Int. Ed. Engl.* **1995**, 34, 259–281.
- 3 G. W. Parshall, S. D. Ittel, *Homogeneous Catalysis*, 2nd ed.; John Wiley & Sons: New York, **1992**.
- 4 B. M. Trost, C. Chan, G. Rühler, *J. Am. Chem. Soc.* **1987**, 109, 3486–3487.
- 5 H. Katayama, M. Nakayama, T. Nakano, C. Wada, K. Akamatsu, F. Ozawa, *Macromolecules* **2004**, 37, 13–17.
- 6 B.M. Trost, M. T. Sorum, C. Chan, A. E. Harms, G. Rühler, *J. Am. Chem. Soc.* **1997**, 119, 698–708.
- 7 C. Yang, S. P. Nolan, *J. Org. Chem.* **2002**, 67, 591–593.
- 8 M. Rubina, V. Gevorgyan, *J. Am. Chem. Soc.* **2001**, 123, 11107–11108.
- 9 C. Bianchini, P. Frediani, D. Masi, M. Peruzzini, F. Zanolini, *Organometallics* **1994**, 13, 4616–4632.
- 10 C. S. Yi, N. Liu, *Organometallics* **1996**, 15, 3968–3971.
- 11 C. Slugovc, K. Mereiter, E. Zobetz, R. Schmid, K. Kirchner, *Organometallics* **1996**, 15, 5275–5277.
- 12 W. T. Boese, A. S. Goldman, *Organometallics* **1991**, 10, 782–786.
- 13 M. Nishiura, Z. Hou, Y. Wakatsuki, T. Yamaki, T. Miyamoto, *J. Am. Chem. Soc.* **2003**, 125, 1184–1185.
- 14 C. S. Yi, N. Liu, A. L. Rheingold, L. M. Liable-Sands, *Organometallics* **1997**, 16, 3910–3913.
- 15 J.-P. Qü, D. Masui, Y. Ishii, M. Hidai, *Chem. Lett.* **1998**, 1003–1004.
- 21 Y. Wakatsuki, H. Yamazaki, N. Kumegawa, T. Satoh, J. Y. Satoh, *J. Am. Chem. Soc.* **1991**, 113, 9604–9610.
- 22 M. O. Albers, D. J. A. de Waal, D. C. Liles, D. J. Robinson, E. Singleton, M. B. Wiege, *J. Chem. Soc., Chem. Commun.* **1986**, 1680–1682.
- 23 J. Le Pailh, F. Monnier, S. Dérien, P. H. Dixneuf, E. Clot, O. Eisenstein, *J. Am. Chem. Soc.* **2003**, 125, 11964–11975.
- 24 J. Le Pailh, S. Dérien, C. Bruneau, B. Demerseman, L. Toupet, P. H. Dixneuf, *Angew. Chem. Int. Ed.* **2001**, 40, 2912–2915.
- 25 J. Le Pailh, S. Dérien, B. Demerseman, C. Bruneau, P. H. Dixneuf, L. Toupet, G. Dazinger, K. Kirchner to be submitted.
- 26 B. M. Trost, A. J. Frontier, *J. Am. Chem. Soc.* **2000**, 122, 11727–11728.
- 27 C. Gemel, G. Kickelbick, R. Schmid, K. Kirchner, *J. Chem. Soc., Dalton Trans.* **1997**, 2113–2117.
- 28 H. Singer, G. Wilkinson, *J. Chem. Soc. (A)* **1968**, 849–853.
- 29 B. M. Trost, S. Matsubara, J.J. Caringi, *J. Am. Chem. Soc.* **1989**, 111, 8745–8746.
- 30 Y. Nishibayashi, M. Yamanashi, I. Wakiji, M. Hidai, *Angew. Chem., Int. Ed.* **2000**, 39, 2909–2911.
- 31 P. J. Fagan, W. S. Mahoney, J. C. Calabrese, I. D. Williams, *Organometallics* **1990**, 9, 1843–1852.

References and Notes to Section 1.5

- 1 C. Bruneau, P. H. Dixneuf, *Acc. Chem. Res.*, **1999**, 32, 311–323.
- 2 C. Bruneau, *Ruthenium vinylidenes and allenylidenes in catalysis in: Ruthenium catalysts and fine chemistry*, Topics in Organomet. Chem., C. Bruneau, P. H. Dixneuf (Eds), Springer, 2004, vol. 11, pp 125–153.
- 3 Y. Sasaki, P. H. Dixneuf, *J. Chem. Soc., Chem. Commun.*, **1986**, 790–791.
- 4 R. Mahé, Y. Sasaki, C. Bruneau, P. H. Dixneuf, *J. Org. Chem.*, **1989**, 54, 1518–1523.
- 5 J. Höfer, H. Doucet, C. Bruneau, P. H. Dixneuf, *Tetrahedron Lett.*, **1991**, 32, 7409–7410.
- 6 J. Ipaktschi, J. Mohsseni-Ala, S. Uhlig, *Eur. J. Inorg. Chem.*, **2003**, 4313–4320.
- 7 H. Doucet, J. Höfer, C. Bruneau, P. H. Dixneuf, *J. Chem. Soc., Chem. Commun.*, **1993**, 850–851.
- 8 H. Doucet, B. Martin-Vaca, C. Bruneau, P. H. Dixneuf, *J. Org. Chem.*, **1995**, 60, 7247–7255.
- 9 H. Doucet, J. Höfer, N. Derrien, C. Bruneau, P. H. Dixneuf, *Bull. Soc. Chim. France*, **1996**, 133, 939–944.
- 10 H. Doucet, N. Derrien, Z. Kabouche, C. Bruneau, P. H. Dixneuf, *J. Organomet. Chem.*, **1997**, 551, 151–157.
- 11 K. Melis, P. Samulkiewicz, J. Rynkowski, F. Verpoort, *Tetrahedron Lett.*, **2002**, 43, 2713–2716.
- 12 L. J. Goossen, J. Paetzold, D. Koley, *Chem. Commun.*, **2003**, 706–707.
- 13 M. Jimenez Tenorio, M. C. Puerta, P. Valerga, F. J. Moreno-Dorado, F. M. Guerra, G. M. Massenet, *Chem. Commun.*, **2001**, 2324–2325.
- 14 M. Picquet, C. Bruneau, P. H. Dixneuf, *J. Chem. Soc., Chem. Commun.*, **1997**, 1201–1202.
- 15 M. Picquet, A. Fernandez, C. Bruneau, P. H. Dixneuf, *Eur. J. Org. Chem.*, **2000**, 2361–2366.
- 16 C. Bruneau, Z. Kabouche, M. Neveux, B. Seiller, P. H. Dixneuf, *Inorg. Chim. Acta*, **1994**, 222, 155–163.
- 17 C. Gemel, G. Trimmel, C. Slugovc, S. Kremel, K. Mereiter, R. Schmid, K. Kirchner, *Organometallics*, **1996**, 15, 3998–4004.
- 18 B. M. Trost, G. Dyker, R. J. Kulaviec, *J. Am. Chem. Soc.*, **1990**, 112, 7809–7811.
- 19 B. M. Trost, R. J. Kulawiec, *J. Am. Chem. Soc.*, **1992**, 114, 5579–5584.
- 20 B. M. Trost, Y. H. Rhee, *J. Am. Chem. Soc.*, **2002**, 124, 2528–2533.
- 21 B. M. Trost, Y. H. Rhee, *J. Am. Chem. Soc.*, **1999**, 121, 11680–11683.
- 22 F. E. McDonald, K. S. Reddy, *J. Organomet. Chem.*, **2001**, 617/618, 444–452.
- 23 M. H. Davidson, F. E. McDonald, *Org. Lett.*, **2004**, 6, 1601–1603.
- 24 W. W. Cutchins, F. E. McDonald, *Org. Lett.*, **2002**, 4, 749–752.
- 25 P. Wipf, T. H. Graham, *J. Org. Chem.*, **2003**, 68, 8798–8807.
- 26 F. E. McDonald, *Chem. Eur. J.*, **1999**, 5, 3103–3106.
- 27 F. E. McDonald, M. M. Gleason, *J. Am. Chem. Soc.*, **1996**, 118, 6648–6659.
- 28 F. E. McDonald, M. M. Gleason, *Angew. Chem. Int. Ed. Engl.*, **1995**, 34, 350–352.
- 29 F. E. McDonald, C. B. Connolly, M. M. Gleason, T. B. Towne, K. D. Treiber, *J. Org. Chem.*, **1993**, 58, 6952–6953.
- 30 M. Tokunaga, Y. Wakatsuki, *Angew. Chem. Int. Ed.*, **1998**, 37, 2867–2868.
- 31 T. Suzuki, M. Tokunaga, Y. Wakatsuki, *Org. Lett.*, **2001**, 3, 735–737.
- 32 P. Alvarez, M. Bassetti, J. Gimeno, G. Mancini, *Tetrahedron Lett.*, **2001**, 42, 8467–8470.
- 33 D. B. Grotjahn, C. D. Incarvito, A. L. Rheingold, *Angew. Chem. Int. Ed.*, **2001**, 40, 3884–3887.
- 34 T. Suzuki, M. Tokunaga, Y. Wakatsuki, *Tetrahedron Lett.*, **2002**, 43, 7531–7533.

2

Asymmetric Hydrocyanation of Alkenes

Jos Wilting and Dieter Vogt

2.1

Introduction

The hydrocyanation of alkenes [1] has great potential in catalytic carbon–carbon bond-formation because the nitriles obtained can be converted into a variety of products [2]. Although the cyanation of aryl halides [3] and carbon-hetero double bonds (aldehydes, ketones, and imines) [4] is well studied, the hydrocyanation of alkenes has mainly focused on the DuPont adiponitrile process [5]. Adiponitrile is produced from butadiene in a three-step process via hydrocyanation, isomerization, and a second hydrocyanation step, as displayed in Figure 1. This process was developed in the 1970s with a monodentate phosphite-based zerovalent nickel catalyst [6].

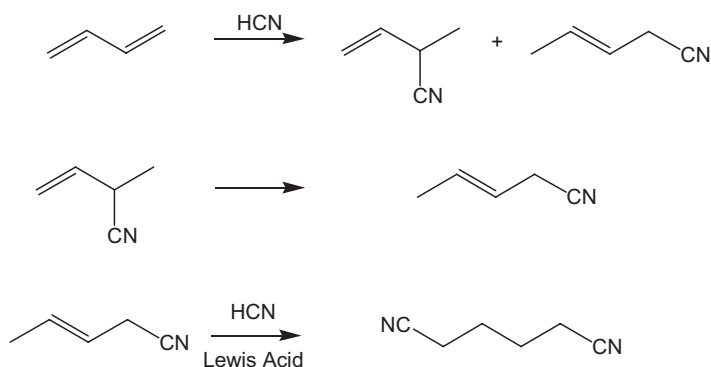


Figure 1. The three-step adiponitrile process.

Although several enzymes can enantioselectively catalyze the hydrocyanation of $R_2C=O$ and $R_2C=NR$ bonds [7], (asymmetric) hydrocyanation of $C=C$ double bonds has no precedents in biology. In homogeneous catalysis asymmetric hydrocyanation is still underdeveloped, as is apparent from the relatively few reports in the literature. In the following paragraphs a short overview will be given divided into the two major substrate classes investigated, cyclic (di)enes and vinylarenes.

2.1.1

Cyclic (Di)enes

In 1979 Elmes and Jackson [8–10] described the asymmetric hydrocyanation of norbornene and norbornadiene, with $\text{Pd}(\text{DIOP})_2$ as catalyst, resulting in *exo*-2-cyanonorbornane. Parker et al. [11, 12] investigated this reaction in more detail and studied the coordination chemistry of $(\text{DIOP})\text{Pd}(\text{C}_2\text{H}_4)$ in the presence of HCN. Under these conditions a hydrido cyano and an alkyl cyano palladium complex were detected by NMR. Takaya et al. [13] applied the phosphine–phosphite ligand binaphos with palladium and nickel and obtained ee (enantiomeric excesses) of 48 % (Pd) and 40 % (Ni) with yields of up to 50 %. Pringle and Baker [14, 15] investigated the phosphite ligand **1**, based on (*R*)-2,2'-binaphthol, with nickel and obtained isolated yields of 40–70 % with ee of 28–38 % (M/L/S/ACH [metal/ligand/substrate/acetone cyanohydrin] 1:2:700:350) at different temperatures. Chan et al. [16] used the diphosphite ligand **2**, based on (*S*)-binaphthol, with nickel and obtained the highest ee, 55.0 %, for hydrocyanation of norbornene; the yield was 89 % (M/L/S/ACH 1:7:100:110).

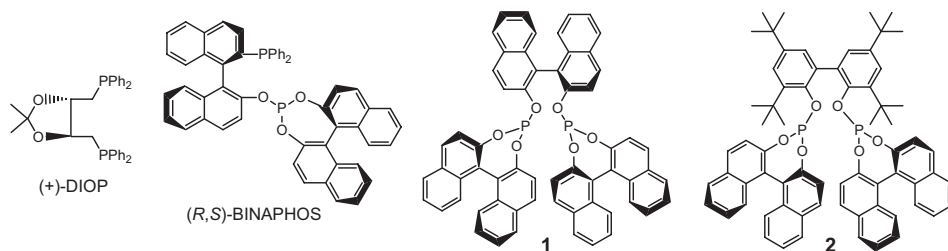


Figure 2. Chiral ligands used in the asymmetric hydrocyanation of norbornene.

2.1.2

Vinylarenes

Chan et al. also tested the $\text{Ni}(\text{ligand } 2)$ system with other substrates, and obtained 50 % ee (89 % yield) in the hydrocyanation of styrene [16]. With $\text{Ni}(\text{cod})_2$ (nickel(0)-bis-[1,5-cyclooctadiene]) in the presence of ligand **3** Babin et al. obtained an ee of 64 % for styrene as substrate, although the regioselectivity of the system was modest (~65 %) [17]. Vogt et al. investigated diphosphonite ligands with an achiral xanthene backbone and binaphthoxy substituents [18]. These resulted in ee of 42 % (styrene), 63 % (4-isobutylstyrene), and 29 % (MVN [6-methoxy-2-vinylnaphthalene]) with ligand **4**.

RajanBabu and Casalnuovo [19, 20] tested diphosphinite ligand systems (**5** and **6** in Figure 4) based on carbohydrate backbones. The steric and electronic properties depended on the substituents on the aryl groups on the phosphorus atoms. The use of different chlorophosphine precursors led to the electronically asymmetric ligand **6**. This approach resulted in both enantiomers of naproxen nitrile from MVN in 91 % ee (*S*)-nitrile (ligand **5**) and 95 % ee (*R*)-nitrile (ligand **6**) at 0 °C.

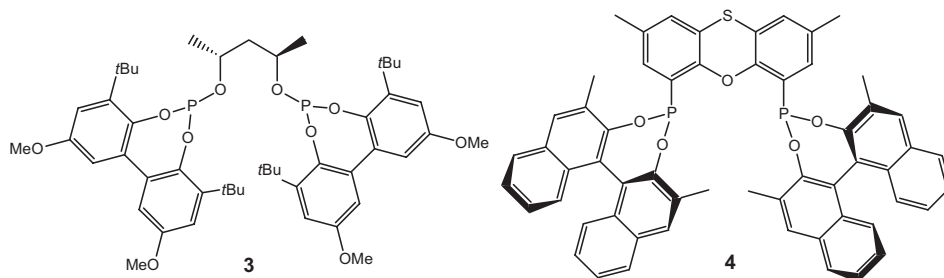


Figure 3. Ligands studied in the asymmetric hydrocyanation of vinylarenes.

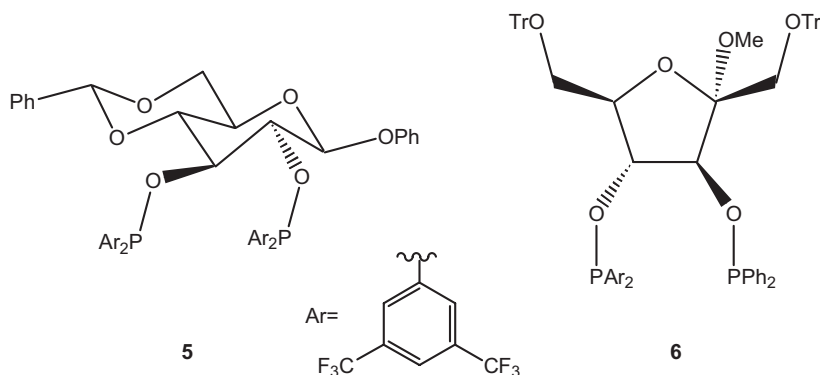


Figure 4. Ligands used by RajanBabu and coworkers.

2.2 Mechanism

Tolman, Druliner, and McKinney [5] were pioneers in nickel-catalyzed hydrocyanation; they used monodentate phosphites mainly to understand and improve the adiponitrile process. Although bidentate ligands give better results in the adiponitrile process [21], mechanistic studies with these systems are rare; bidentate phosphinites have been studied in the asymmetric hydrocyanation of MVN [19].

The hydrocyanation of ethylene with a monodentate ligand has been shown to have zero-order rates in substrate and in HCN but second-order in catalyst [22]. The possible intermediate $[(L)Ni(CN)(C_2H_3)(C_2H_4)]$ has been characterized by NMR, leading to the conclusion that reductive elimination is the rate-determining and most important step. During this step an additional ligand would need to recombine with this nickel species resulting in a second-order rate law in catalyst. This is based on the fact that five-coordinated nickel complexes are more effective than the four-coordinated complexes in the reductive elimination [23].

Accordingly, it seems plausible that the reductive elimination step in the catalytic cycle with bidentate ligands (**F** to **E** in Figure 5) follows an associative mechanism in which first an alkene or nitrile (displayed as S) coordinates to the nickel,

thereby stabilizing the zero-valent complex **E**, which is formed during the reductive elimination. Complex **E** can then exchange **S** for HCN (resulting in **B**) or the substrate (resulting in **D**). Labeling studies with deuterated MVN [19] and 2M3BN (2-methyl-3-butenenitrile) [24] revealed an equilibrium between species **F** and **C** in the catalytic cycle. Proton migration (**C** to **F** or **H**) is favored to the branched species **F** by the η^1 – η^3 equilibrium (**F**–**G**), which is not possible for the linear species **H**. Although several η^3 -benzylic complexes have been characterized [25, 26], the (α -methyl)benzylic cyano complex (**G**) could not be isolated or even observed. The η^3 – η^1 equilibrium has been investigated for an aliphatic allyl cyano nickel(II) complex [27].

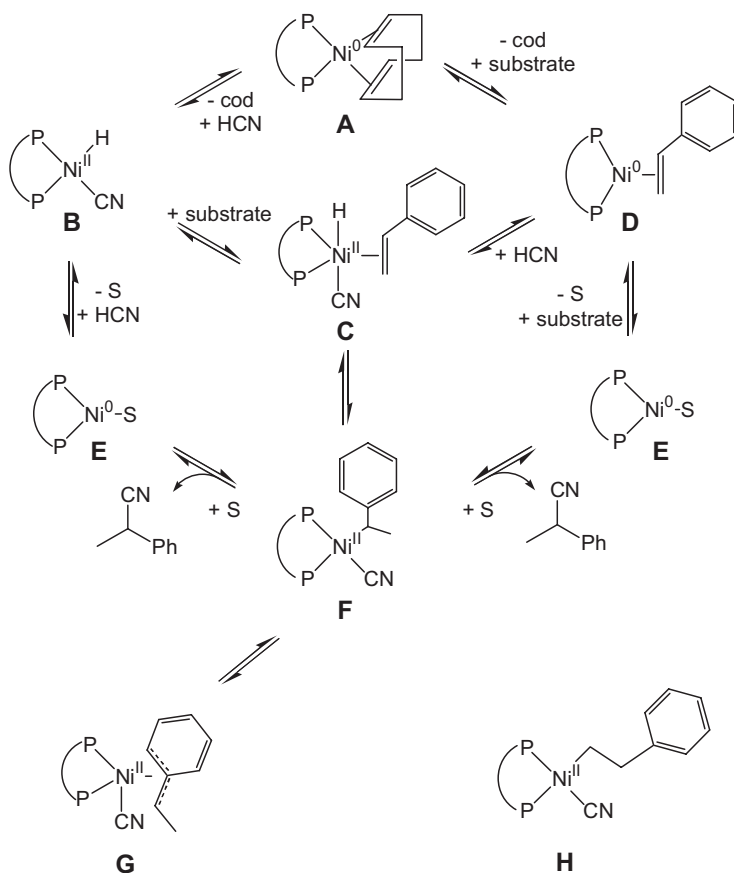


Figure 5. The catalytic cycle of hydrocyanation of styrene as example of the vinylarenes.

For hydrocyanation of MVN with bidentate phosphinites zero-order in substrate and in HCN was again observed. Yet first-order in catalyst was obtained because of the bidentate ligand. The hydrocyanation followed in time should, in theory, fit a simple zero-order model ($d[\text{RCN}]/dt = k_1[\text{Ni}]$). The catalyst is, however,

deactivated in time, by formation of an insoluble dicyanonickel complex $(PP)Ni(CN)_2$, making deactivation of the catalyst an important issue. The kinetic model is, therefore, more consistent with the experimental data when both zero-order product formation ($d[RCN]/dt = k_1[Ni]$) and deactivation ($-d[Ni]/dt = k_2[HCN][Ni]$) are used, as is displayed in Figure 6.

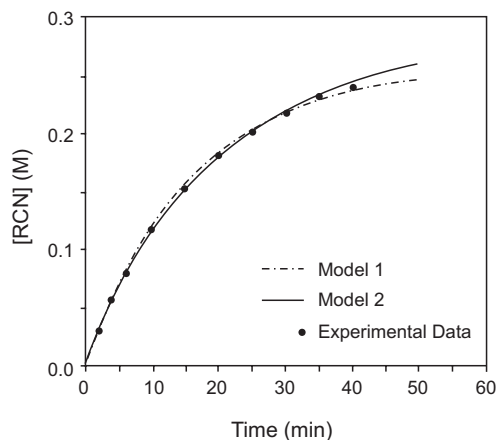


Figure 6. The hydrocyanation of MVN, kinetic model 1: $d[RCN]/dt = k_1[Ni]$ and $-d[Ni]/dt = k_2[HCN][Ni]$ with $k_1 = 27 \text{ min}^{-1}$ and $k_2 = 0.15 \text{ M}^{-1} \text{ min}^{-1}$. This figure is reprinted from Ref. 19. Copyright 1994 American Chemical Society.

Several other interesting effects have been observed in the reductive elimination and hydrocyanation reactions. The bite angle [28] has a significant effect in the reductive elimination. A 10^4 fold rate increase was observed progressing from a small bite angle ($\sim 85^\circ$) to a larger bite angle in $(DIOP)Pd(CH_2TMS)CN$ ($\sim 100^\circ$, TMS = trimethylsilyl) [29]. The rate depends on the alkyl group, causing it to vary by orders of magnitude ($CH_2CMe_3 \sim 10 \times CH_2TMS \gg CH_3$). Addition of the Lewis acid $AlPh_3$ increases the rate by a factor of 50 [30].

The electronic properties of the phosphorus groups affect the activity and stability of the catalyst during the hydrocyanation. Diphosphine and diphosphinite catalyst systems benefit greatly from electron-withdrawing substituents on the aryl groups [19, 31]. Benzene, toluene, and hexane [32] are usually the solvents of choice, coordinating solvents, for example CH_3CN , have been shown to have a negative effect, resulting in a dramatic drop in yield and ee. The effect of the HCN source (either directly as HCN or in situ via ACH), has not been studied carefully. The concentration of free HCN is much lower when ACH is used, leading to less deactivation. The role of the acetone formed during the reaction has not been determined, however. On the other hand a low concentration of HCN can also be achieved by slowly bubbling HCN through the reaction mixture or by adding an HCN solution by syringe pump [33].

2.3

Scope and Limitations

In asymmetric hydrocyanation reactions the desired isomers are the chiral branched products only. Good regioselectivity toward the branched product (>98 %) is limited to vinylarenes. Hydrocyanation of 1,3-dienes gives a variety of mixtures depending on the catalyst and conditions; 1-alkenes give the linear nitrile as major product [34]. Both are seen in the adiponitrile process in which the unwanted branched 2M3BN (hydrocyanation product from 1,3-butadiene) is isomerized to the linear product 3-pentenitrile, which is then hydrocyanated by in-situ isomerization to 4-pentenitrile, resulting in the linear adiponitrile. Thus vinylarenes and cyclic alkenes (mainly norbornene) are usually the substrates of choice for the asymmetric hydrocyanation. Hopefully 1,3-dienes will become feasible substrates in the near future.

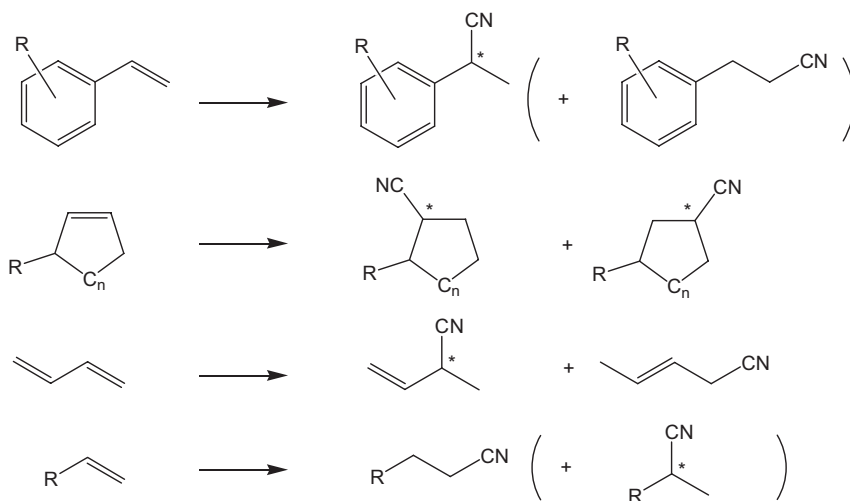


Figure 7. Substrate variations in asymmetric hydrocyanation (minor products between brackets).

The poor turn-over numbers (TON) in the hydrocyanation reactions are another limitation, because of degradation of the catalyst, which still has to be overcome. The maximum TON reached so far have been in the order of 500–750, which is extremely low compared with other homogenous catalytic reactions.

Experimental

The preparative synthesis of the (*S*) nitrile described here was originally reported by RajanBabu and Casulnuovo [19]; the synthesis of the (*R*) nitrile is reported elsewhere [20].

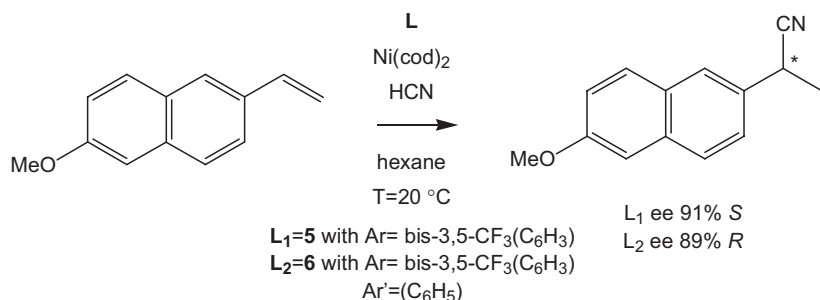


Figure 8. The asymmetric hydrocyanation of MVN.

Caution! HCN is a highly toxic, volatile liquid (bp $27\text{ }^{\circ}C$) that is also susceptible to explosive polymerization in the presence of base catalysts. It should be handled only in a well-ventilated fume hood and by teams of at least two technically qualified persons who have received appropriate medical training for treating HCN poisoning. Sensible precautions include having available proper first aid equipment and HCN monitors. Uninhibited HCN should be stored at a temperature below its melting point ($-13\text{ }^{\circ}C$). Excess HCN may be disposed by addition to aqueous sodium hypochlorite, which converts the cyanide to cyanate.

All reactions are carried out under inert atmospheres using standard Schlenk techniques. All solvents are dried and distilled before use. $Ni(cod)_2$ is extremely air-sensitive, especially in solution, and thermally unstable. $Ni(cod)_2$ [35], $(Et_2N)PCl_2$ [36], 3,5-bis-(trifluoromethyl)bromobenzene, and (–)-phenyl-4,6-*O*-benzylidene- β -D-glucopyranoside are commercially available.

Bis[3,5-bis(trifluoromethyl)phenyl]chlorophosphine

A 1.0 M solution of [3,5-bis(trifluoromethyl)phenyl]magnesium bromide is prepared by slow addition of 18.5 g (60 mmol) 3,5-bis-(trifluoromethyl)bromobenzene in 40 mL THF to a slurry of Mg turnings in 20 mL THF. This is stirred for 1 h at $20\text{ }^{\circ}C$ and, after filtration, slowly added to a solution of 5.0 g (29 mmol) $(Et_2N)PCl_2$ in 30 mL THF at $0\text{ }^{\circ}C$. After stirring for 2 h the mixture obtained is concentrated in vacuo. Cyclohexane (100 mL) is added and the mixture is filtered through celite resulting in a solution of bis[3,5-bis(trifluoromethyl)phenyl](diethylamino)phosphine. Dry HCl is passed through this solution for 1 h (a solution of HCl in diethyl ether, which is commercially available, can also be used). After filtration and concentration, 12.4 g (88 %) of the chlorophosphine can be collected as a white solid. $^{31}P\{^1H\}$ NMR (C_6D_6): δ 70.4 (s)

Preparation of Ligand 5

A solution of $(3,5-(CF_3)_2C_6H_3)_2PCl$ (1.246 g, 2.53 mmol) in 5 mL CH_2Cl_2 is cooled to $0\text{ }^{\circ}C$ and added dropwise to a solution of phenyl 4,6-*O*-benzylidene- β -D-glucopyranoside (0.397 g, 1.15 mmol) and dimethylaminopyridine (0.030 g, 0.25 mmol)

in 15 mL CH_2Cl_2 /pyridine (1:1) at 0 °C. The reaction mixture is warmed to room temperature, stirred overnight, and concentrated to dryness in vacuo. Hot benzene is added to the resulting solids and the mixture is filtered. The filtrate obtained is concentrated in vacuo to a dry white solid. This white solid is then washed with 2 mL cold hexane and dried in vacuo to give 1.135 g (79 %) ligand 5. $^{31}\text{P}\{^1\text{H}\}$ NMR (C_6D_6): δ 108.4 (s, 1P), 107.5 (s, 1P).

Hydrogen Cyanide (HCN) [37]

Iron(II)sulfate heptahydrate (1.9 g) is added to 125 mL sulfuric acid. This solution is heated under an argon stream to 80 °C. Subsequently a solution of 96.5 g KCN (1.49 mol) in 200 mL H_2O is added by syringe pump during 2 h and the gaseous HCN produced is led over CaCl_2 after which it is condensed in a thick glass bottle at -78 °C. The argon, which might contain traces of HCN, is led through a solution of 100 mL 35 % H_2O_2 and 60 g KOH in 200 mL H_2O , which neutralizes the cyanide. Yield: ~20 mL (35 %). Instead of condensing the HCN it is also possible to use the HCN–argon mixture immediately in the catalytic hydrocyanation reaction.

Preparative Asymmetric Hydrocyanation of MVN

To a solution of $\text{Ni}(\text{cod})_2$ (0.059 g, 0.22 mmol) and 5 (0.271 g, 0.22 mmol) in 10 mL hexane is added 4.00 g MVN (21.7 mmol) and 110 mL hexane. An approximately 2 M solution of HCN in toluene (11 mL, 22 mmol) is added to the resulting slurry within 2.5 h by using an addition funnel or syringe pump. The initially heterogeneous solution becomes an orange–brown homogenous solution about halfway through the addition after which the product will precipitate as a white powder. Conversion can be monitored by GC analysis and if the reaction does not go to completion additional HCN solution can be added slowly. The original report showed ~94 % conversion. The reaction is stirred overnight, purged with argon for 5 min to remove traces of HCN, and then benzene is added to dissolve all of the solids.

After concentration of the reaction mixture in vacuo, hexane (200 mL) is added and the product is collected by filtration (yield 3.5 g of an off-white solid). The filtrate is then concentrated in vacuo to about 50 mL to isolate a second crop of product by filtration, (yield 0.5 g). A third crop of product can be isolated by flash chromatographic work-up (silica) of the filtrate (90:10 hexane– Et_2O), yield 0.4 g, total yield 4.4 g (96 %). Recrystallization from boiling 10 % ether–hexanes results in optically pure (*S*)-nitrile (occasionally it may be necessary to perform a second recrystallization). Mp 99–100 °C, $[\alpha]_{\text{D}}^{23} = -29.4 \pm 0.8^\circ$ ($c=1$) Enantiomeric excess can be measured by HPLC (Chiracel OJ column with 5 % isopropanol–hexane as eluent (flow rate 1 mL min⁻¹) at 40 °C, retention times (min): MVN 28.52, (*S*)-nitrile 32.87, (*R*)-nitrile 40.60).

References and Notes

- 1 Huthmacher, K.; Krill, S. Reactions with hydrogen cyanide (hydrocyanation). In *Applied Homogeneous Catalysis with Organometallic Compounds*, 2nd edn; Cornils, B., Hermann, W. A., Eds.; Wiley-VCH: Weinheim, 2002; Vol. 1 pp 465–486.
- 2 Pollak, P.; Romeder, G.; Hagedorn, F.; Gelbke, H. Nitriles. In *Ullman's Encyclopedia of Industrial Chemistry*, 5th edn; Wiley-VCH: Weinheim, 1985–1996; Vol. A17 pp 363–376.
- 3 Sundermeier, M.; Zapf, A.; Beller, M. *Eur. J. Inorg. Chem.* **2003**, (19), 3513–3526.
- 4 Groger, H. *Chem. Eur. J.* **2001**, 7 (24), 5246–5251.
- 5 Tolman, C. A.; McKinney, R. J.; Seidel, W. C.; Druliner, J. D.; Stevens, W. R. *Adv. Catal.* **1985**, 33, 1–46.
- 6 Drinkard, W. C. Hydrocyanation of olefins using selected nickel phosphite catalysts. US 3,496,215, **1970**.
- 7 Gregory, R. J. H. *Chem. Rev.* **1999**, 99 (12), 3649–3682.
- 8 Elmes, P. S.; Jackson, W. R. *J. Am. Chem. Soc.* **1979**, 101 (20), 6128–6129.
- 9 Elmes, P. S.; Jackson, W. R. *Aust. J. Chem.* **1982**, 35 (10), 2041–2051.
- 10 Jackson, W. R.; Lovel, C. G. *Aust. J. Chem.* **1982**, 35 (10), 2053–2067.
- 11 Hodgson, M.; Parker, D. J. *Organomet. Chem.* **1987**, 325 (1/2), C27–C30.
- 12 Hodgson, M.; Parker, D.; Taylor, R. J.; Ferguson, G. *Organometallics* **1988**, 7 (8), 1761–1766.
- 13 Horiuchi, T.; Shirakawa, E.; Nozaki, K.; Takaya, H. *Tetrahedron: Asymmetry* **1997**, 8 (1), 57–63.
- 14 Baker, M. J.; Pringle, P. G. *J. Chem. Soc., Chem. Commun.* **1991**, (18), 1292–1293.
- 15 Baker, M. J.; Harrison, K. N.; Orpen, A. G.; Pringle, P. G.; Shaw, G. *J. Chem. Soc., Chem. Commun.* **1991**, (12), 803–804.
- 16 Yan, M.; Xu, Q. Y.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2000**, 11 (4), 845–849.
- 17 Babin, J. E.; Whiteker, G. T. Asymmetric syntheses using optically active metal–ligand complex catalysts. US 5,360,938, **1994**.
- 18 Goertz, W.; Kamer, P. C. J.; Van Leeuwen, P. W. N. M.; Vogt, D. *Chem. Eur. J.* **2001**, 7 (8), 1614–1618.
- 19 Casalnuovo, A. L.; Rajanbabu, T. V.; Ayers, T. A.; Warren, T. H. *J. Am. Chem. Soc.* **1994**, 116 (22), 9869–9882.
- 20 Rajanbabu, T. V.; Casalnuovo, A. L. *J. Am. Chem. Soc.* **1996**, 118 (26), 6325–6326.
- 21 Kreutzer, K. A.; Tam, W. Hydrocyanation process and multidentate phosphite and nickel catalyst composition therefore. US 5,663,369, **1997**.
- 22 McKinney, R. J.; Roe, D. C. *J. Am. Chem. Soc.* **1985**, 107 (1), 261–262.
- 23 Tatsumi, K.; Nakamura, A.; Komiya, S.; Yamamoto, A.; Yamamoto, T. *J. Am. Chem. Soc.* **1984**, 106 (26), 8181–8188.
- 24 Druliner, J. D. *Organometallics* **1984**, 3 (2), 205–208.
- 25 Gatti, G.; Lopez, J. A.; Mealli, C.; Musco, A. J. *Organomet. Chem.* **1994**, 483 (1/2), 77–89.
- 26 Albers, I.; Alvarez, E.; Campora, J.; Maya, C. M.; Palma, P.; Sanchez, L. J.; Passaglia, E. J. *Organomet. Chem.* **2004**, 689 (4), 833–839.
- 27 Brunkan, N. M.; Jones, W. D. *J. Organomet. Chem.* **2003**, 683 (1), 77–82.
- 28 Casey, C. P.; Whiteker, G. T. *Isr. J. Chem.* **1990**, 30 (4), 299–304.
- 29 Marccone, J. E.; Moloy, K. G. *J. Am. Chem. Soc.* **1998**, 120 (33), 8527–8528.
- 30 Huang, J.; Haar, C. M.; Nolan, S. P.; Marccone, J. E.; Moloy, K. G. *Organometallics* **1999**, 18 (3), 297–299.
- 31 Goertz, W.; Keim, W.; Vogt, D.; Englert, U.; Boele, M. D. K.; Van der Veen, L. A.; Kamer, P. C. J.; Van Leeuwen, P. W. N. M. *J. Chem. Soc., Dalton Trans.* **1998**, (18), 2981–2988.
- 32 The catalyst precursor is not very soluble in hexane and gives a slurry which becomes homogenous during catalysis
- 33 The slow addition of HCN to the reaction mixture is very important;

we obtained good results using a syringe pump to add the HCN solution

- 34 Goertz, W.; Kamer, P. C. J.; Van Leeuwen, P. W. N. M.; Vogt, D. *Chem. Commun.* **1997**, (16), 1521–1522.
- 35 Schunn, R. A. *Inorg. Synth.* **1974**, 15, 5–9.
- 36 Whitaker, C. M.; Kott, K. L.; McMahon, R. J. *J. Org. Chem.* **1995**, 60 (11), 3499–3508.
- 37 Slotta, K. H. *Berichte d. D. Chem. Gesellschaft* **1934**, 67, 1028–1030.

III

C–H Transformation at sp^2 -hybridized Carbon Atoms

1

C–H Transformation at Arenes

1.1

Direct Oxidation of Arenes to Phenols and Quinones

Vsevolod V. Rostovtsev

Dedicated to Professor John E. Bercaw on the occasion of his 60th birthday.

1.1.1

Introduction

Direct oxidation of arenes to phenols is a difficult reaction with enormous potential for both synthetic and industrial chemistry. Although metallation of arenes, whether with main group or transition metals, to give compounds with metal–aryl bonds is very common, a one-step transformation of benzene C–H bonds to C–OH bonds is not nearly as widespread. Many complexes capable of arene C–H bond activation do not survive under the oxidizing conditions required for hydroxylation. When metal–carbon bonds are actually formed during catalysis, transformation of Ar–M bonds to Ar–OH bonds requires not only a robust catalyst but also a selective oxidant as well as acceptable rates of ligand exchange. Although the aromatic π -system is an attractive target for an electrophilic attack, it is with rare exceptions less reactive towards radicals and nucleophiles, limiting potential approaches to arene hydroxylation. Furthermore, since phenols are more electron-rich than the starting materials, overoxidation is a problem. Several approaches have been used to overcome these problems and the solutions are detailed below.

1.1.2

Radical Hydroxylations

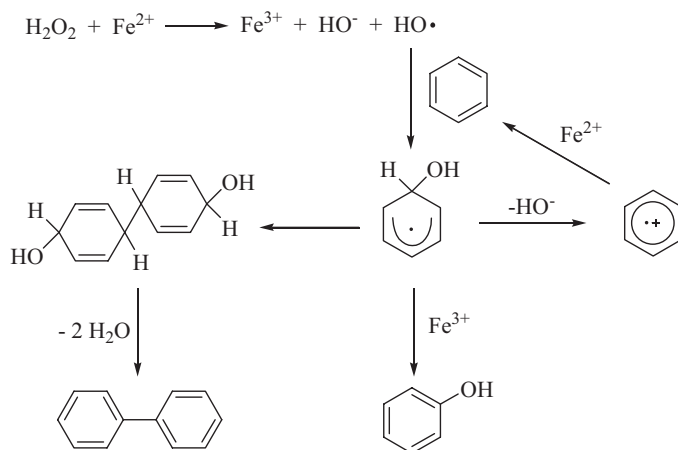
The first example of the direct hydroxylation of arenes to phenols was reported in 1900 and described oxidation of benzene with a mixture of iron(II) sulfate and hydrogen peroxide (Fenton's reagent) [1]. Low yields of phenol (21 % yield based on H_2O_2) are typically obtained in such cases, in addition to significant amounts of biphenyl (24 % yield based on H_2O_2) [1–3]. Both selectivity to phenol and overall

yield can be improved by using oxidants stronger than iron(III) [2]. With copper(II), for example, the yield of phenol increases to 57 % and the ratio of phenol to biphenyl improves to 140:1. Similar results are obtained with the peroxydisulfate/iron(II) system [4]. Electrocatalytic hydroxylation coupled with continuous extraction also gives better yields of phenols [5]. Udenfriend's reagent is another iron(II)-based system capable of radical arene hydroxylation. Molecular oxygen in combination with ascorbic acid is used as the oxidant in Udenfriend's system [6, 7]. Molecular oxygen can also be used directly in combination with copper(I) in aqueous sulfuric acid, although the yield of phenol is low (24 %) and a significant amount of hydroquinone is formed at the same time (8 % yield) [8, 9]. Photochemically generated hydroxyl radicals can also be used for arene hydroxylation [10].

The distinguishing feature of all these systems is the generation of a highly reactive hydroxyl radical which is responsible for arene hydroxylation (Scheme 1) [11–13]. The radical is produced in the reaction between hydrogen peroxide and an iron(II) ion, or any other transition metal ion with a suitable redox potential. Next, the hydroxyl radical adds to an arene molecule and produces a hydroxycyclohexadienyl intermediate, which has been observed experimentally under the reaction conditions [14]. Several pathways are available for further transformation of the radical – oxidation to phenol with iron(III) or other oxidant; dimerization followed by dehydration to afford biphenyl and loss of HO^- to give an aromatic radical cation, which can be reduced back to starting material by iron (II); or dimerization followed by dehydration to afford biphenyl. With some substrates (*e.g.* phenylacetic acid) elimination or rearrangement of the aromatic side chains is also observed [2]. The exact fate of the hydroxycyclohexadienyl radical depends on the acidity of the reaction media and on the nature of the oxidants present in the system. Typically, a mixture of phenols and biphenyls is formed. With copper(II) or excess of iron(III) present, the oxidation step is favored and higher yields of phenol are observed, along with better selectivities. The acidity of the reaction mixture also plays a role – the phenol/biphenyl ratio increases with decreasing pH. The same mechanistic manifold can also be accessed in the hydroxylation of arenes with peroxydisulfates.

In more general terms, a review of product yields and distributions in radical hydroxylations shows that a great variety of yields and selectivities can be achieved by careful manipulation of experimental conditions. Occasionally, formation of biphenyl, which is often regarded as indicating the presence of a radical-based process, can be completely suppressed. Therefore, it is very risky to make statements about the mechanism of hydroxylation based solely on product distributions and without thorough mechanistic investigations [11].

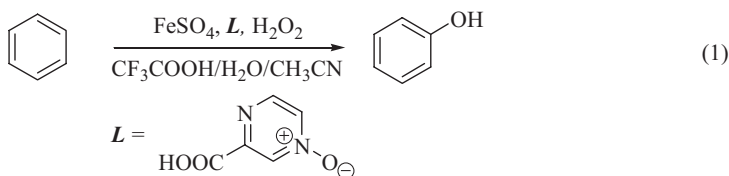
Compared with the starting arenes, phenols are more reactive toward the hydroxyl radical, resulting in overoxidation to quinones and decreasing selectivity and yield of the reaction. Physical separation of products from the starting materials by means of a biphasic reaction mixture can be successfully used in this case [15]. Yields as high as 80 % (based on benzene) have been reported with cetyl-



Scheme 1

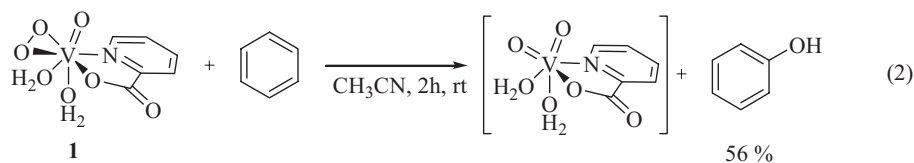
trimethylammonium bromide phase-transfer catalyst (0.67 mol%) and iron(III) nitrate (0.33 mol%), using 0.5 M hydrogen peroxide (50 mol%) in a water–benzene mixture at pH 3 and 50 °C. No overoxidation was observed, and the source of extra oxidizing equivalents (0.8 equiv phenol formed with 0.5 equiv H_2O_2) was not discussed in the original work.

Further improvement of the $\text{Fe(II)}/\text{H}_2\text{O}_2$ system was recently reported by Bianchi [16–18]. Selectivity and yield were greatly improved by using a pyrazine-carboxylate ligand (Eq. 1). Physical separation of the oxidant (H_2O_2) from the products, achieved by using a biphasic system, with careful optimization of the auxiliary pyrazine-carboxylate ligand and of reaction conditions, greatly improved selectivity (78 % based on H_2O_2 and 85 % based on benzene) and conversion (up to 8.6 % based on benzene) of the phenol synthesis. The best results were obtained with 3-carboxypyrazine-*N*-oxide.

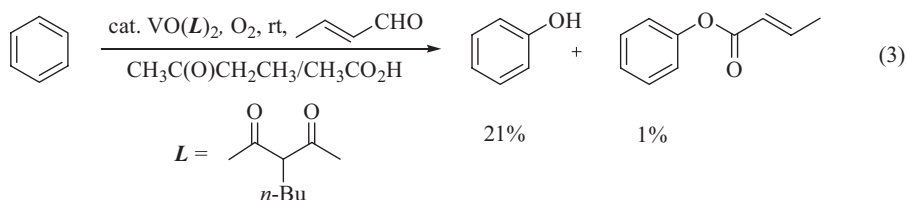


Although significant improvements have been made in the synthesis of phenol from benzene, the practical utility of direct radical hydroxylation of substituted arenes remains very low. A mixture of *ortho*-, *meta*- and *para*-substituted phenols is typically formed. Alkyl substituents are subject to radical H-atom abstraction, giving benzyl alcohol, benzaldehyde, and benzoic acid in addition to the mixture of cresols. Hydroxylation of phenylacetic acid leads to decarboxylation and gives benzyl alcohol along with phenolic products [2]. A mixture of naphthols is produced in radical oxidations of naphthalene, in addition to diols and hydroxyketones [19].

In 1983, Mimoun and co-workers reported that benzene can be oxidized to phenol stoichiometrically with hydrogen peroxide in 56 % yield, using peroxo-vanadium complex **1** (Eq. 2) [20]. Oxidation of toluene gave a mixture of *ortho*-, *meta*- and *para*-cresols with only traces of benzaldehyde. The catalytic version of the reaction was described by Shul'pin [21] and Conte [22]. In both cases, conversion of benzene was low (0.3–2 %) and catalyst turned over 200 and 25 times, respectively. The reaction is thought to proceed through a radical chain mechanism with an electrophilic oxygen-centered and vanadium-bound radical species [23].



Hydrogen peroxide can be replaced by molecular oxygen in vanadium-catalyzed hydroxylations of arenes, as first reported by Mukaiyama (Eq. 3) [24]. Improved versions were later described by Battistel (VCl_3 /ascorbate) [25] and Shul'pin ($(n\text{-Bu})_4\text{NVO}_3$ /pyrazine-2-carboxylic acid/ascorbic acid) [26]. It is noteworthy that a molecular oxygen/sacrificial reductant (crotonaldehyde, zinc, or ascorbate) combination was used (*cf.* Udenfriend's reagent above) and that the mechanism is most likely to involve hydroxyl radicals.

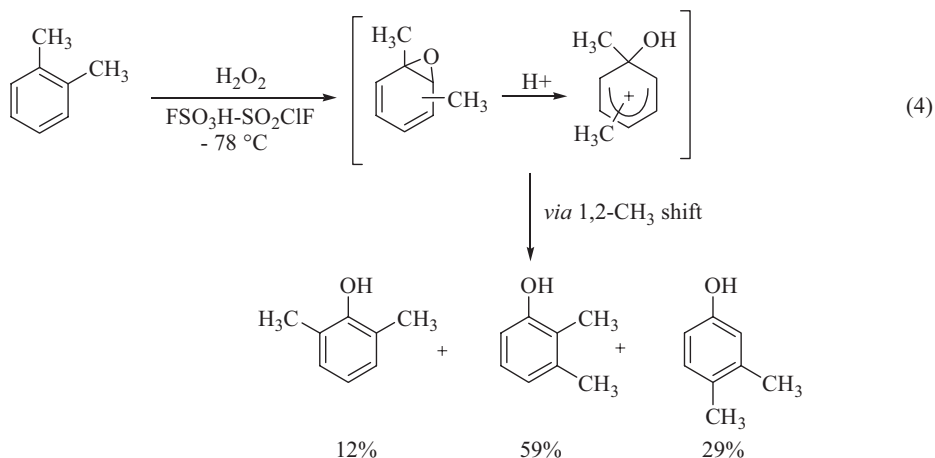


1.1.3

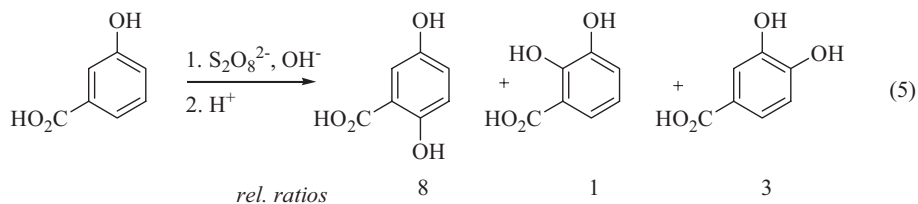
Electrophilic Hydroxylations

Electrophilic hydroxylation of arenes with hydrogen peroxide proceeds in low yield and is hampered by phenol overoxidation. The yield and selectivity improve when either a strong Brønsted (HF , FSO_3H – SO_2ClF) [27] or Lewis (AlCl_3) [28] acid is used. These reagents associate with phenolic oxygen and discourage further hydroxylation. In the former case, benzene was converted to phenol in 54–67 % yield. With substituted arenes, mostly *ortho* and *para* isomers were obtained in 43–82 % yields. With xylenes, migration of the methyl group during hydroxylation was observed (Eq. 4), in line with the proposed formation of hydroxyarenium intermediates.

Electron-rich arenes, for example phenols, anisoles, and arylamines, can be hydroxylated with potassium persulfate in basic media [29]. Hydroxylation of phe-



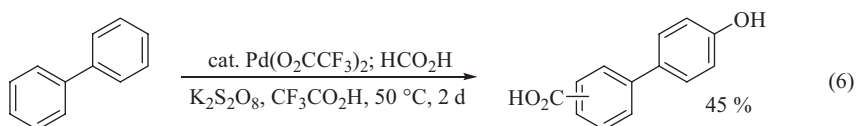
nols and anisoles is known as the Elbs oxidation (Eq. 5) [30]. The process is performed at high pH and results in the formation of an aryl sulfate ester which is hydrolyzed in a separate step. The yields are moderate and *para*-substitution is usually preferred. Alcohols, aldehydes, and olefins are tolerated in this process. The reaction is thought to proceed via electrophilic attack of persulfate on the phenolate ion.



Hydroxylation of arylamines with persulfate ion, or Boyland–Sims oxidation, gives *ortho*-substituted aminophenols in good yields [29]. As with the Elbs oxidation, the procedure is also carried out in two steps – first, treatment with the oxidant to obtain an aminophenyl sulfate ester and, second, hydrolysis to obtain the final product. Primary, secondary and tertiary amines can all be used in this reaction. The *ortho* product is formed, except when no *ortho*-positions are available, which leads to *para*-substitution. Electrophilic attack on the *ipso*-carbon is believed to be the most likely mechanism, although minor radical pathways also seem to be present.

Hydroxylations of electron-rich arenes (phenols and hydroxyarenes) can be achieved catalytically with $(P-P)Pt(CF_3)_3X$ and H_2O_2 (where $P-P$ is dppe and X is $(CH_2Cl_2)ClO_4$) [31]. The *ortho*- and *para*-isomers are formed, with *ortho* substitution preferred. The authors propose that the higher yields of *ortho*-hydroxylated products are a manifestation of catalyst pre-coordination.

Palladium-catalyzed hydroxylation of benzene to phenol with oxygen can be accomplished by use of a sacrificial co-reductant, for example carbon monoxide [32, 33]. The reaction is carried out in acetic acid under 15 atm dioxygen and 15 atm carbon monoxide at 180 °C giving phenol in 25 % yield. The catalyst is a mixture of $\text{Pd}(\text{O}_2\text{CCH}_3)_2$ and 1,10-phenanthroline. Carbon monoxide serves as an oxygen atom acceptor and can be replaced with dihydrogen [34]. Carbon dioxide and water, respectively, are formed as by-products. The use of a co-reductant can be avoided altogether if heteropolyacids are used as co-catalysts [35]. The scope of these processes is still mainly limited to benzene, although a rare example of hydroxylation-carboxylation of biphenyl with catalytic $\text{Pd}(\text{O}_2\text{CCF}_3)_2$, giving a mixture of 3' and 4'-hydroxybiphenylcarboxylic acids, was recently reported [36]. Formic acid was used as a carbonyl source and potassium peroxysulfate as oxidant (Eq. 6).

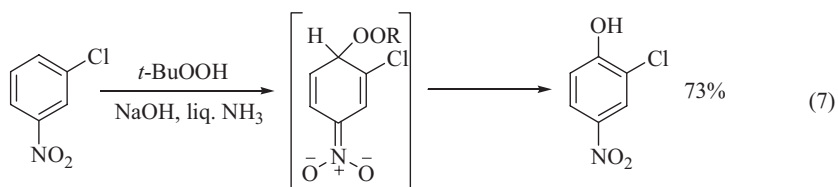


Although the exact mechanism of palladium-catalyzed hydroxylations is unclear at the moment, it is very likely that palladium-aryl intermediates, formed by electrophilic arene activation, are on the reaction pathway [36–38]. In some cases, it has been shown that molecular oxygen is the ultimate source of the element in phenol. Formation of the carbon–oxygen bond might happen in several different ways: (1) insertion of an oxygen atom into a $\text{Pd}-\text{Ar}$ bond then ligand exchange; (2) reductive elimination from $\text{Ar}-\text{Pd}^{\text{II}}-\text{OAc}$ species, then hydrolysis; or (3) oxidation to $\text{Ar}-\text{Pd}^{\text{IV}}-\text{OR}$ then reductive elimination and hydrolysis. It is conceivable that the presence of carbon monoxide or hydrogen ensures that palladium is present in the catalytically active oxidation state. Clearly, further mechanistic work is needed in this area.

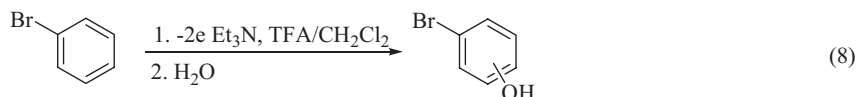
1.1.4

Nucleophilic Hydroxylations

Arenes activated with an electron-withdrawing group may react with alkyl peroxides directly, by nucleophilic attack at the *ortho*- or *para*-position. Nitroarenes can be hydroxylated with alkyl hydroperoxides in strongly basic media in moderate to good yields (Eq. 7) [39].



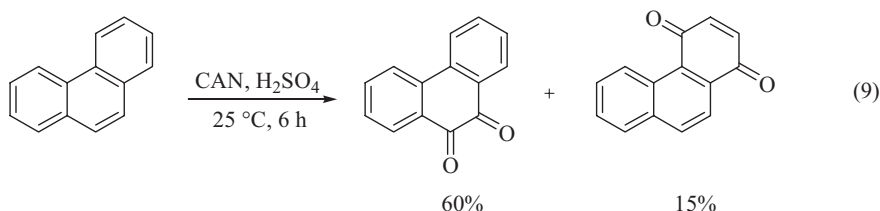
Electron-poor arenes can be converted into phenols by anodic oxidation [40]. A mixture of *ortho*-, *meta*- and *para*-substituted phenols is obtained in 18–89 % yields (Eq. (8); TFA is trifluoroacetic acid). Aryl trifluoroacetate is formed first and then hydrolyzed to phenol in a separate step. The oxidation potential of phenyl trifluoroacetate is higher than that of phenol, which explains the absence of overoxidation.



1.1.5

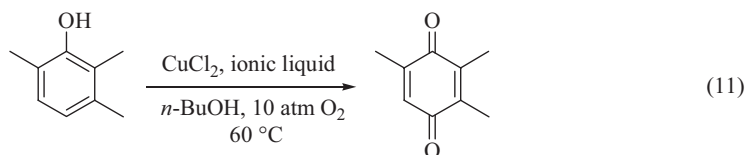
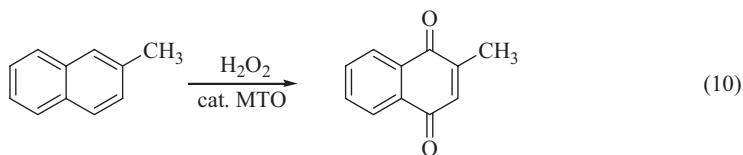
Direct Synthesis of Quinones from Arenes

The direct oxidation of arenes to quinones is a reaction with a limited scope [41]. Only substrates that form stable quinones give good yields. For example, oxidation of anthracene to stable 9,10-anthraquinone with chromic acid is practiced on industrial scale. Such oxidations are believed to proceed through a series of one-electron oxidation/solvolysis steps. Yields and selectivity may be improved by using a strong one-electron oxidant such as cerium ammonium nitrate (CAN), as in the oxidation of phenanthrene to phenanthrenequinones (Eq. 9) [42].



Use of transition metal catalysts opens up previously unavailable mechanistic pathways. With hydrogen peroxide and catalytic amounts of methyl trioxorhenium (MTO), 2-methylnaphthalene can be converted to 2-methylnaphtha-1,4-quinone (vitamin K₃ or menadione) in 58 % yield and 86 % selectivity at 81 % conversion (Eq. 10) [43, 44]. Metalloporphyrin-catalyzed oxidation of 2-methylnaphthalene with KHSO₅ can also be used to prepare vitamin K₃ [45]. The MTO-catalyzed process can also be applied to the synthesis of quinones from phenols [46, 47]. In particular, several benzoquinones of cardanol derivatives were prepared in this manner [48]. The oxidation is thought to proceed through the formation of arene oxide intermediates [47].

Recently, a copper-catalyzed synthesis of trimethyl-1,4-benzoquinone, a key intermediate in the industrial synthesis of vitamin E, has been reported (Eq. 11) [49]. In the proposed mechanism, a tetranuclear cluster $[\text{Cu}_4(\mu^4\text{-O})\text{Cl}_{10}]^+$, isolated from the reaction mixture, deprotonates phenol and oxidizes it to a copper-bound phenolate radical, which reacts with dioxygen.



Experimental

2-Methylnaphtha-1,4-quinone

H₂O₂ (85 %, 14.3 mL, 0.49 mmol) was added dropwise at room temperature to a solution of 10.0 g (70.3 mmol) 2-methylnaphthalene and 0.349 g (1.4 mmol) methyltrioxorhenium in 150 mL acetic acid. The reaction mixture was stirred at 40 °C for 4 h under a N₂ atmosphere and then 100 mL water was added. The mixture was extracted with CH₂Cl₂ (3 × 100 mL). The combined organic phases were washed with 150 mL water, dried over Na₂SO₄, and concentrated at 20–40 °C/10–20 Torr. The conversion was 81 % (GC–MS). The quinone products were separated from the starting material by column chromatography (silica gel 32–63 μm mesh). Recrystallization of the chromatographed product from ethanol afforded the quinone in >98 % purity and 58 % yield (5.65 g).

1.2

Metalation of Arenes

1.2.1

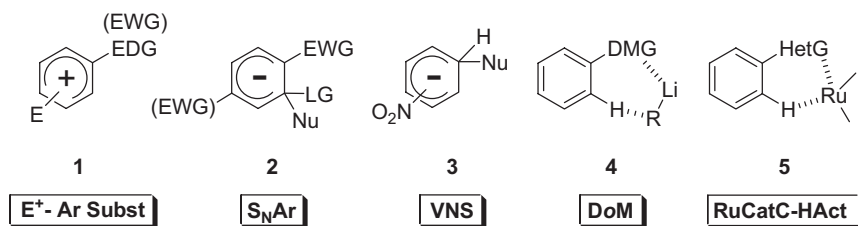
Directed ortho and Remote Metalation (DoM and DreM)

Victor Snieckus and T. Macklin

1.2.1.1 Introduction and Fundamental Concepts

For the chemist practicing polysubstituted aromatic and heteroaromatic synthesis, methods steeped in classical electrophilic (1, Scheme 1) [1] and nucleophilic substitution [2] and S_{RN}1 (2) [3] reactions have been joined and, not infrequently superseded, by vicarious substitution (3) [4] and by DoM (4) [5] processes. The Murai ortho CH activation (5) [6] is a recently evolving and potential competitive method to the DoM tactic. The 60 years since its discovery by Wittig and Gilman, and 40 years since its systematic study by the school of Hauser, the DoM reaction has advanced by the contributions of Christensen, Beak, Meyers, and many other

groups[5] of fundamental and dependable directed metalation groups (DMG) (Table 1) which provide this chemistry with broad carbo- and heteroatom-based functional group scope for synthetic manipulation of aromatic structures.



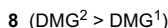
Scheme 1

Table 1. Hierarchal order of DMGs and test conditions for their DoM.

	DMG	Base	Solvent	Additive	Temp., °C
Increasing Directing Ability ↑	CONR ₂	<i>s</i> -BuLi	THF	TMEDA	−78
	SO _(1,2) <i>t</i> -Bu	<i>n</i> -BuLi	THF	none	−78
	CONR ₂	<i>s</i> -BuLi	THF	TMEDA	−78
	CONLiR	<i>n</i> -BuLi	THF or Et ₂ O	TMEDA or none	−78 to reflux
	SO ₂ NR ₂	<i>n</i> -BuLi	THF	none	−78 to 0
	SO ₂ NLiR	<i>n</i> -BuLi	THF	none	−10 to 25
		<i>n</i> -BuLi or <i>s</i> -BuLi	THF or Et ₂ O	none	−45 to 0
	CO ₂ Li	<i>s</i> -BuLi	THF	TMEDA	−90
	OMOM	<i>n</i> -BuLi or <i>t</i> -BuLi	Et ₂ O	none	−20 to 25
	NLi(BOC)	<i>t</i> -BuLi	THF	none	−50 to −20
	NLi(Piv)	<i>n</i> -BuLi	THF	none	−40 to 0
	F	<i>n</i> -BuLi	Et ₂ O	none	< −50

In comparison with E⁺ and Nu[−] aromatic substitution methods, mild conditions, incontestable ortho regioselectivity, and, perhaps most significant, post-DoM synthetic potential are the hallmarks of the DoM reaction. E⁺ reactions are controlled by the normal EDG/EWG ortho, para/meta directing effects, occur under harsh acidic conditions[7], and invariably require separation of the resulting mixtures of isomers; Nu[−] S_{RN}1 processes are highly dependent on EWG situated ortho/para to the displaceable LG. The potential of the vicarious Nu[−] substitution in aromatic synthetic chemistry remains to be broadly implemented[4]. Although complementary to E⁺ and Nu[−] substitution, the DoM process has features and advantages for adoption and application in synthesis as follows:

- The sequential, sometime one-pot, introduction of two similar or different electrophiles enables the preparation of contiguously substituted aromatics which are rare in catalogs and difficult to prepare by alternative methods (6, Scheme 2) [8].



Scheme 2

- The cooperative nature of two similar or different meta-related DMG enables DoM at the in-between site thus constituting a different route to continuous 1,2,3-substitution patterns (7) [9]. The analogous *meta* and *para*-related DMG isomers provide routes, most of which have not been tested, to other patterns which are a function of their relative hierarchy qualitatively established by inter- or intramolecular competition experiments (Scheme 3) [5].

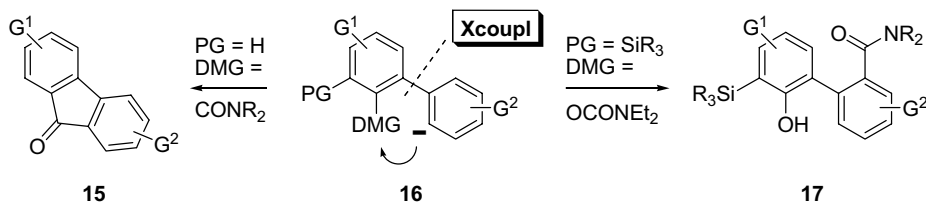


Scheme 3

- The DoM-mediated introduction of a DMG² to the existing DMG¹ offers the opportunity to take advantage of the more powerful (e.g. DMG²) for a walk-around-the-ring metalation excursion (8) [10].
- Aside from its summit position as a DMG (10, Scheme 3) the OCONet₂ provides versatile anionic aromatic chemistry: anionic ortho-Fries rearrangement (9, Scheme 3) [11], a useful synthetic step by itself but also one that provides a path, after incipient phenol protection, to further DoM, resulting in a 1,2,3-substituted aromatic derivative (9 → 12, see also Scheme 13) [12]; homo-ortho-Fries rearrangement to aryl acetamides (10 → 11) providing a route to benzofuranones which are difficult to prepare by Friedel–Crafts-based strategies [9]; intra-

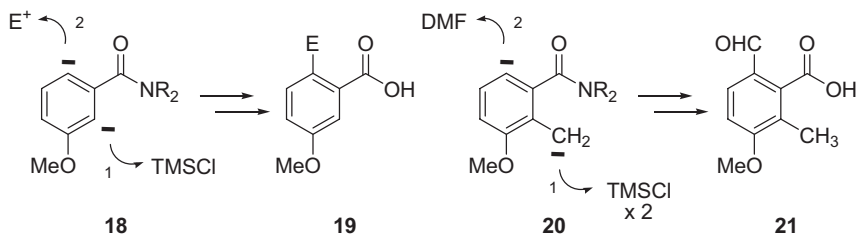
molecular carbamoyl transfer in an ortho-acetyl system, **10** → **14**, constituting a modern variant of the Baker–Venkataraman reaction [13]; and **10** → **13**, a key step in general chromanone preparation which has also found application in total synthesis (see Scheme 15) [14].

- Directed remote metalation (DreM) of biaryl amides and O-carbamates, conceptually based on the complex-induced proximity effect (CIPE) [15] provides, especially in view of their link to transition metal-catalyzed cross coupling regimens [16], general and versatile routes to fluorenones (**16** → **15**, Scheme 4) [5, 17] and biaryl amides (**16** → **17**) [18] whose features are overriding Friedel–Crafts reactivity and yield enhancement in comparison to Suzuki–Miyaura coupling routes for highly hindered biaryls, respectively. Additional features of the O-carbamate DreM result is potential further DoM of **17** with appropriate phenol protection and cyclization to dibenzopyranones [18].



Scheme 4

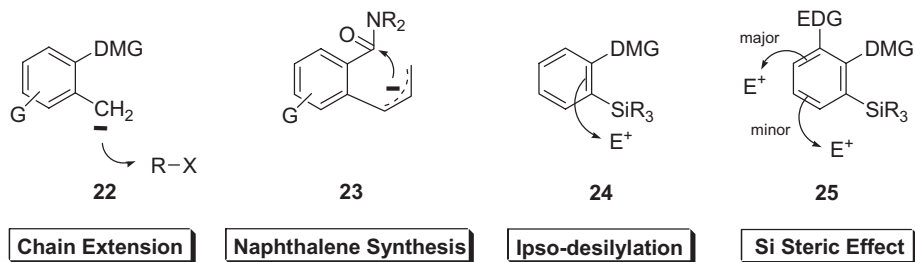
- Introduction of RLi-unreactive silicon substituents has advantages in protection of Ar–C–H and Ar–CH₃ sites. Thus taking advantage of the cooperativity of amide and methoxy DMG, metalation–silylation followed by metalation–E⁺ quench affords, after fluoride-mediated desilylation and amide hydrolysis, a route 1,2,5-substituted benzoic acids, **18** → **19** (Scheme 5). Lateral metalation, of considerable utility in post-DoM chain extension [19], followed by double silylation and further DoM–E⁺ quench and the same fluoride and acid treatment steps, furnishes 1,2,3,4-tetrasubstituted aromatic compounds, **20** → **21** [10, 20].



Scheme 5

- Once introduced, a methyl group has enhanced acidity on many DMG systems and is amenable, by LDA-mediated deprotonation to chain extension and heteroannulation processes [21]. In a route as yet not investigated for potential, DoM followed by magnesium transmetalation and allylation enables convenient

access to derivatives which on LDA-induced cyclization provide routes to oxygenated naphthalenes, **23** (Scheme 6) [22].



Scheme 6

- Silicon group introduction by DoM also provides opportunity for design of E^+ -induced ipso-desilylation and sterically determined reactions. In the former, the operation of a β -cation effect induces rate enhancements in ipso-substitution in systems which are unreactive (EWG) or para-reactive (EDG) toward typical electrophilic reagents (**24**). The presence of strong EDG overrides the β -cation effect but the bulk of the silane increases the ortho/para ratio which enables development of substitution patterns and types which are not easily derived by classical electrophilic reaction means (**25**) [23].

1.2.1.2 Mechanism

The status, detailed in the excellent comprehensive review by Clayden[5a], and supplemented by coverage of the complex-induced proximity effect (CIPE) [15] may be summarized by the following, at times conflicting, points.

1.2.1.2.1 Kinetics

Large kinetic-isotope effects (KIE) for $DMG = CONR_2$ and CON^+R suggest tunneling during proton transfer and may be interpreted that DoM proceeds by fast reversible complexation (CIPE) followed by slow deprotonation. Kinetic and IR studies and direct observation of a complex in the α -deprotonation of *N,N*-dimethylbenzamide may be taken as indirect evidence for a CIPE in DoM. For $DMG = OMe$, KIE are much lower but show no evidence of prior $BuLi-OMe$ coordination and may suggest that only the acidifying effect of OMe as a σ -EWG group drives the DoM reaction. The competitive efficiencies of deprotonation for 2-quinolone (C-8), *N,N*-diisopropylbenzamide, and 2-TMS-*N,N*-diisopropylbenzamide (C-6), 32,000:1800:1 respectively, are indicative of strong geometrical dependence of the DoM process. In contrast, a study on a series of benzyl alcohols suggests an out-of-plane relationship for favorable DoM.

1.2.1.2.2 NMR and Calculations

^1H and ^{13}C NMR studies show that for $\text{DMG} = \text{CH}_2\text{NMe}_2$, species occur as mixtures of three different dimers with strong intramolecular chelation which is maintained in the monomer on addition of TMEDA. ^6Li and ^1H NMR studies on $\text{DMG} = \text{OMe}$, NMe_2 show that, although a tetrameric anisole- $n\text{-BuLi}$ complex is formed, it is unreactive and that only by addition of TMEDA does DoM proceed via an $(n\text{-BuLi})_2$ TMEDA/anisole complex. Ab-initio calculations on $\text{DMG} = \text{OMe}$, OR systems support minimum RO-Li interactions and lead to the conclusion that inductive effects are of great significance and that precomplexation is not a factor in DoM (transition state **28**, Scheme 7) [24]. MNDO calculations for $\text{DMG} = \text{CONR}$ suggest that agostic Li-H interactions are important in prelithiation structures and provide indirect evidence for CIPE.

1.2.1.2.3 Solvent and Additive Effects

Direct observation of complex in the α -deprotonation of *N,N*-dimethylbenzamide and kinetic studies are interpreted in terms of a tetrameric cube-like transition state structure typical of solid-state RLi structures in which ligands bound to the Li centers facilitate the release of the α -carbanion species. The continuing existence of the RLi tetramer on addition of TMEDA contrasts with the dogma that this additive breaks up aggregates and is rationalized by TMEDA advancing the formation of the α -carbanion in the transition state analogous to the effect of the R carbanion character in the tetramer.

1.2.1.2.4 X-ray Structural Analysis

The solid-state structure of the species $\text{DMG} = \text{CH}_2\text{NMe}_2$ is a tetramer in which each Li atom is associated with three carbanion carbons and one nitrogen atom. Similar analysis of *N,N*-diisopropylbenzamide and 1-naphthamide shows that in the solid state the bulky amide substituent, being unable to bridge the amide carbonyl O with ortho-C via a single Li atom, escapes into bridged dimer structures in which one Li is planar with the amide and the other is planar with the aromatic ring.

1.2.1.2.5 Current Mechanistic Picture

Setting aside the lively debate regarding CIPE vs kinetically enhanced deprotonation [15], the emerging picture is that the DoM reaction involves two steps, complex formation and deprotonation. Which effect predominates is a function of the DMG – for strong DMG, e.g. CONR_2 , CIPE predominates and geometry effects are significant; for weak DMG, e.g. OMe, coordination is electronically or geometrically impossible and inductive effects are responsible for the acidity of the ortho-hydrogen. For both, steric effects will, as expected, also play a role. The interconversion of organolithium homo- into hetero-aggregates also plays a role in observed structural and reactivity differences [25].

1.2.1.3 Scope and Limitations

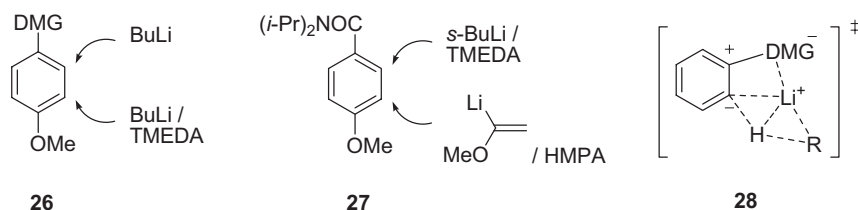
1.2.1.3.1 Directed Metalation Groups (DMG)

For fast and efficacious DoM, the best DMG will combine strong Lewis-base character for coordination to Li and robust inductive effect for ortho-H acidification. The CIPE concept may be invoked as a controlling element of regioselectivity by altering the coordination/induction balance. Not to be denied is the consideration that the most powerful DMG also are also electrophilic groups, e.g. OCONR_2 and CO_2^- , which must be denied reactivity by low temperature, deactivation (e.g. CON^-R), and steric effect considerations (or combinations of these, e.g. N^-Boc , N^-Piv). DMG = halogen plays an important role in heteroaromatic DoM [26]. Use of DMG = Br, I, but not Cl for DoM of aromatic compounds is plagued by metal–halogen exchange or DoM followed by benzyne formation when RLi reagents are used. Regioselectivity can, however, be achieved by CIPE in dihalogen systems and LiNR_2 reagents do not participate in metal–halogen exchange processes. For the synthetic chemist the critical action is usually DMG manipulation into useful functional groups and target molecules.

The relative power of DMG (Table 1), established by experiments at low temperature and short reaction times and thus crudely representative of kinetic control conditions, may vary with inter- and intramolecular competition, conditions, and sometimes results are conflicting. Nevertheless, for synthetic practice this hierarchy follows a qualitative order consistent with CIPE and serves as a useful predictive chart. For thermodynamic control conditions, the pK_a chart of Fraser of 12 DMG [27], determined by equilibrium deprotonation using LiTMP ($\text{pK}_a = 37.8$), is a guide for lithium dialkylamide DoM reactions.

1.2.1.3.2 Analysis of Competing DMG

Coordination and inductive effects of DMG will also be affected by base, solvent, and additives. Illustrative of rationalizations for regiochemical consequence are **26** and **27** (Scheme 7). For both systems, **26**, under conditions of BuLi, coordination (CIPE) dominates with the consequence of deprotonation ortho to the stronger Lewis base site while under BuLi/TMEDA conditions the alkyllithium is complexed to the basic TMEDA (and THF) and, hence, coordination effects are mimized, acidifying effects are significant, and deprotonation occurs ortho to the more electronegative, therefore more Lewis-acidifying, OMe group. A similar rationale is suggested for the base-dependent difference in regioselectivity for **27**.



DMG = NMe_2 , CH_2NMe_2

Scheme 7. Analysis of competing DMGs.

1.2.1.3.3 Compatible Functional Groups

As expected, functional group tolerance in the strongly basic alkyllithium or lithium dialkylamide DoM reaction is limited to non-electrophilic, nonacidic, and non-metal halogen exchange type groups (inter alia, CO_2R (at times), OR, SR, Cl, SiR_3 , all DMG). Mixed Zn and Al bases may in the future overcome some of these drawbacks [28]. Once introduced, useful functionality requires either in situ (e.g. $\text{CHO} \rightarrow \text{CH}(\text{OLi})\text{NR}_2$) or separate protection. Retention of recalcitrant DMG until the end of a synthetic sequence may be advisable (e.g. $\text{CONEt}_2 \rightarrow \text{CO}_2\text{H}$). Introduction of an ortho-bromo substituent by DoM provides a masked latent anion which may be revealed by metal-halogen exchange subsequent to manipulation of the molecule by unrelated chemistry [29].

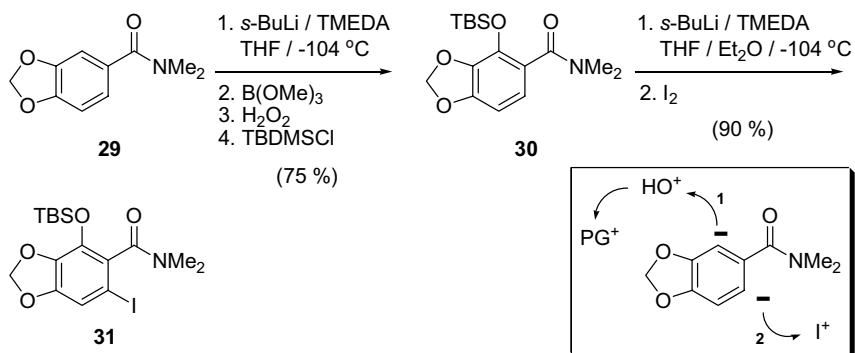
1.2.1.3.4 Initial Test Conditions

Random but fairly extensive literature analysis enables production of a rough guide for the test DoM experimental conditions as a function of DMG (Table 1). In practice, variation of all commercially available RLi and LiNR_2 reagents, additives, solvents, and temperature is the norm.

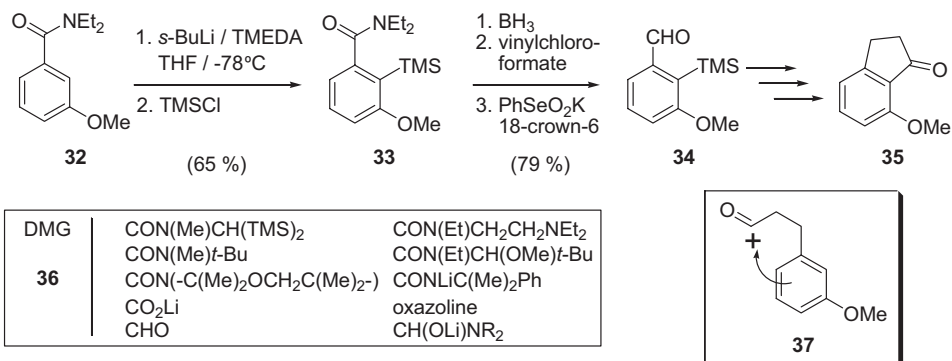
1.2.1.4 DoM Methodology for Substituted Aromatics

Selected examples demonstrate the methodological value of DoM. The conversion $29 \rightarrow 30 \rightarrow 31$ (Scheme 8) shows the merit of in-between metalation, OH^+ synthetic equivalent introduction, and metalation-mediated iodination to overcome the inability of electrophilic iodination owing to the presence of a new EDG [30].

The sequence $32 \rightarrow 33 \rightarrow 34 \rightarrow 35$ (Scheme 8) also illustrates in-between DoM but, in addition, the important conversion of amides into more useful FG and a method to override the normal Friedel-Crafts reactivity by use of a carbo-desilylation reaction (37) [31]. Amide DMG which have been tested in developing methods for conversion to corresponding acid derivatives and masked aldehyde DMG and the parent carboxylic acid are useful to consider (36).

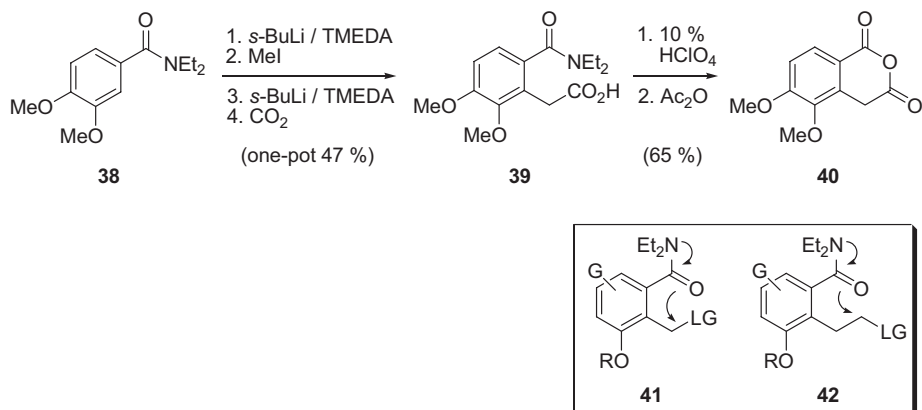


Scheme 8

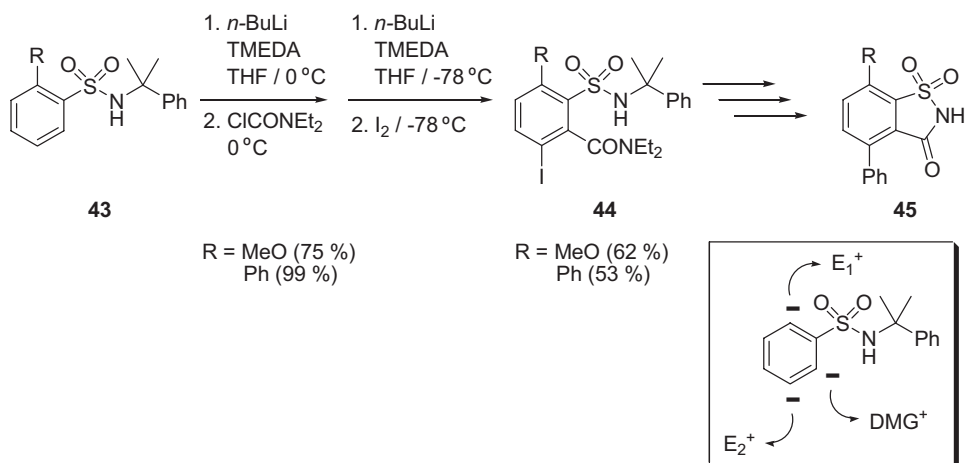


Scheme 9. Overriding Friedel–Crafts regiochemistry. Amides as precursors to more useful derivatives.

Chain extension methodology, **38** \rightarrow **39** \rightarrow **40** (Scheme 9) enables abbreviated preparation of systems which are difficult by classical, usually electrophilic substitution chemistry (**40**) [32] and heterannulation strategies **41**, **42** [19, 33].

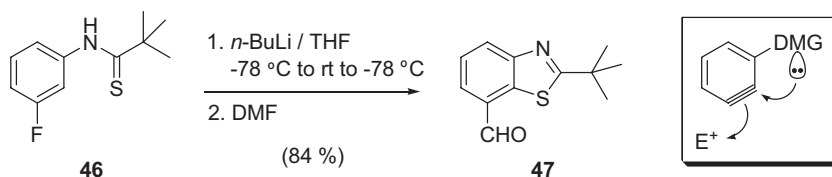
Scheme 10. DoM of benzamide followed by *o*-tolyl carboxylation.

Sulfonamide DoM in conjunction with cross coupling chemistry, **43** → **44** → **45** (Scheme 10) is instructive for double DoM sequences followed by further advantage of an introduced DMG [34].



Scheme 11. Sequential Do of N-cumylsulfonamide and amide DMGs. Synthesis of 4,7-substituted saccharins.

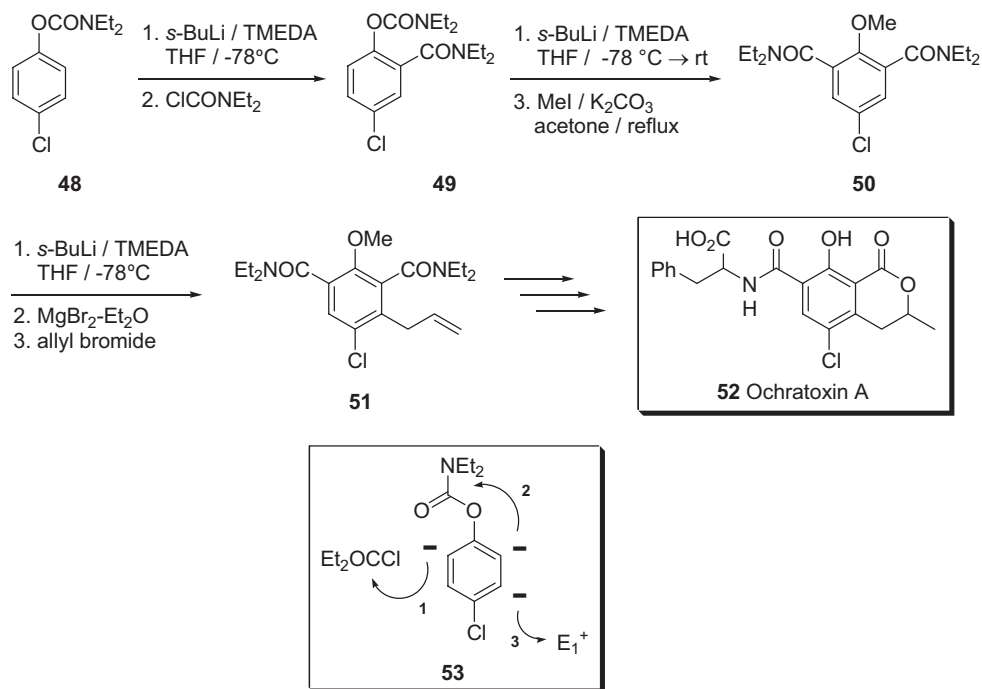
The advantage of in-between DoM followed by sequential intramolecular trapping of the incipient benzyne and electrophile quench, **46** → **47** (Scheme 11) constitutes a powerful method in heteroaromatic synthesis [35].



Scheme 12

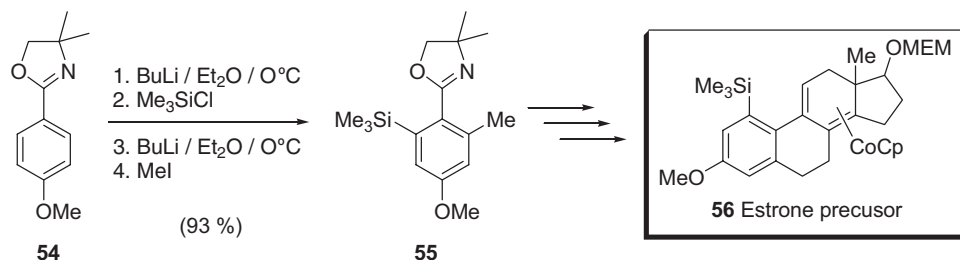
1.2.1.5 DoM in Total Synthesis

Total synthesis has benefited from key DoM reactions. The sequence **48** → **49** → **50** → **51** (Scheme 12) en route to the natural product ochratoxin A (**52**) takes multiple advantage of anion chemistry (**53**) ortho-metalation of the powerful OCONEt₂ group (step 1), anionic Fries rearrangement (step 2), in-between DoM and chain-extension by Li-Mg transmetalation (step 3) [12].



Scheme 13. ArOCONEt₂ DoM / ortho-Fries strategy towards the total synthesis of ochratoxin A.

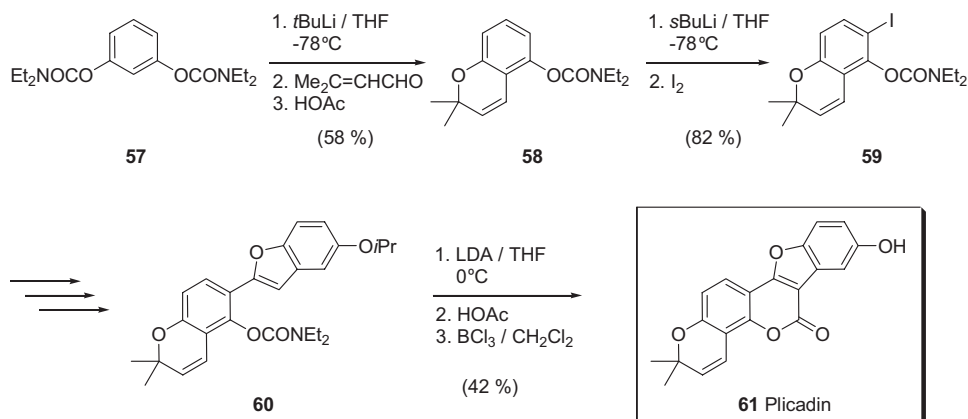
2,6-Disubstitution via DoM, 54 → 55 (Scheme 14) constitutes an efficient starting point in the synthesis of the estrone precursor 56 [36].



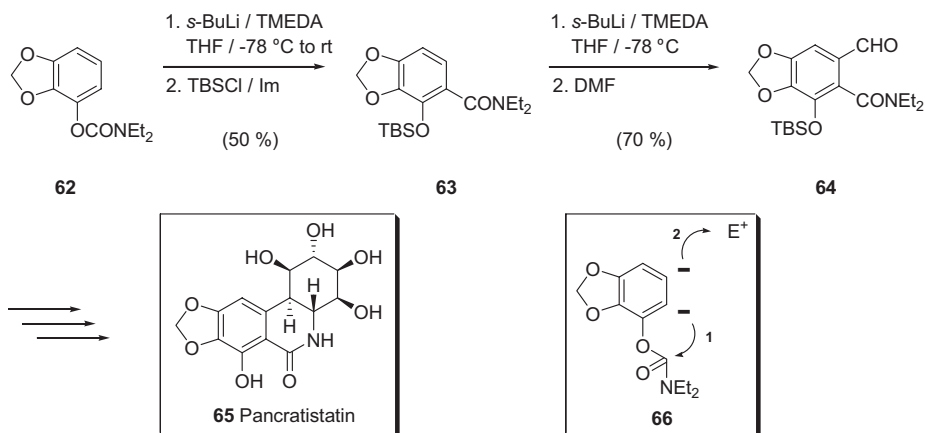
Scheme 14. Sequential DoM using oxazoliny DMG towards the synthesis of co-steroidal complexes.

The route toward the purported natural product, plicadin [14] (61, Scheme 15) incorporates in-between DMG metalation-regioselective chromene construction (57 → 58), further DoM (→ 59), a Sonogashira–Castro Stephens sequence (→ 60), and an efficient key DreM-based concluding step.

The synthesis of pancratistatin [37] (65, Scheme 15), involving anionic ortho-Fries (62 → 63) and further DoM (→ 64) is a pertinent showcase of anionic chemistry for preparation of a pentasubstituted aromatic using the conceptual framework 66.

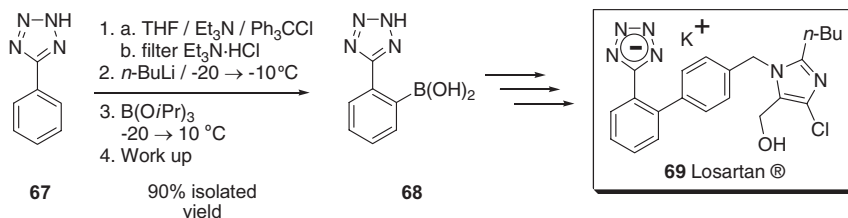


Scheme 15. total synthesis of plicadin.



Scheme 16. Total synthesis of pancratistatin.

The synthesis of the angiotensin II inhibitor Losartan [38] (**69**, Scheme 16) fittingly illustrates the impact of DoM on current large-scale industrial practice. The powerful tetrazolyl DMG (**67**) is used in a 4-step sequence without isolation of intermediates to afford boronic acid **68** which, via a key Suzuki–Miyaura cross coupling, leads the commercial medicinal agent in multi-ton quantities.

Scheme 17. DoM of *N*-tritylphenyltetrazole applied to industrial scale synthesis of losartan.

Experimental

2-Phenyl-4-phenanthrol [22]

MeLi (3.4 mL, 4.8 mmol, 1.4 M in Et₂O) was added to a stirred solution of *o*-(2-phenylallyl)-*N,N*-diisopropyl-naphthamide (0.9 g, 2.4 mmol) in anhydrous THF (50 mL) at -78 °C under argon. The solution turned black immediately. The reaction mixture was left to warm to ambient temperature overnight, quenched with saturated aqueous NH₄Cl (50 mL) and the aqueous phase was extracted with Et₂O (3 × 50 mL). The combined organic layer was evaporated to dryness and the residue was purified by flash column chromatography on silica gel (4:1 hexanes–Et₂O) to afford 2-phenyl-4-phenanthrol (0.59 g, 90 %) as a light brown solid.

5-Chloro-*N*¹,*N*¹,*N*³,*N*³-tetraethyl-2-methoxyisophthalamide, 50 (Scheme 13) [12]

A solution of 4-chloro-2-(diethylcarbamoyl)phenyl diethylcarbamate **49** (2.06 g, 8.7 mmol) in anhydrous THF (10 mL) was added to a stirred solution of *sec*-BuLi (13.8 mL, 19.14 mmol, 1.39 M in cyclohexane) and TMEDA (2.9 mL, 19.14 mmol) in THF (170 mL) maintained at -78 °C under a nitrogen atmosphere. The stirred reaction mixture was left to warm to room temperature overnight and treated with satd aq NH₄Cl. The THF was removed under reduced pressure and the remaining solution was extracted with Et₂O (3 × 25 mL). The aqueous layer was acidified with 2 M HCl (pH 3), and the whole mixture was extracted with Et₂O–CH₂Cl₂ (1:1, 3 × 25 mL) and concentrated under reduced pressure to give 1.7 g of a solid that was heated under reflux with a mixture of MeI (10 mL, 22.8 mmol) and K₂CO₃ (3 g, 24.6 mmol) in acetone (30 mL) for 20 h. Standard workup followed by flash column chromatography on silica gel (1:1, EtOAc–hexane) afforded **50** (0.976 g, 42 %) as a colorless oil.

9-Isopropoxyplcadine (Scheme 15) [14]

To a stirred solution of freshly prepared LDA (4.367 mmol) in THF (5 mL) at 0 °C was added, via a cannula, a solution of 2,2-dimethyl-5-(*N,N*-diethyl-*O*-carbamoyl)-6-(2-(isopropoxy)benzo[*b*]furan)-2*H*-1-benzopyran **60** (398 mg, 0.89 mmol) in THF (20 mL). After 15 min, the reaction mixture was concentrated under reduced pressure and AcOH (15 mL) was added. The stirred mixture was heated to reflux for 10 min, cooled, CH₂Cl₂ (20 mL) and H₂O (10 mL) were added, and the organic layer was separated, dried (Na₂SO₄), and concentrated under reduced pressure. Flash column chromatography (EtOAc–hexanes 1.5:8.5) afforded 9-isopropoxyplcadine (376 mg, 84 %) as a yellow solid.

1.2.2

Electrophilic Metalation of Arenes

Vladimir V. Grushin

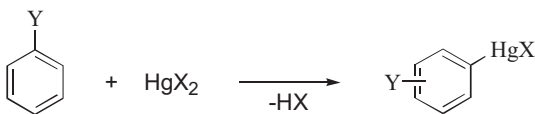
1.2.2.1 **Introduction**

Discovered over a century ago, electrophilic mercuration is probably the oldest known C–H bond-activation reaction with a metal compound. The earliest examples of aromatic mercuration were reported by Volhard (mercuration of thiophene) [1], Pesci (mercuration of aromatic amines) [2], and Dimroth [3], who was the first to mercurate benzene and toluene, generalize the reaction, and assign the correct structures to the products originally observed by Pesci. Since the work of Dimroth electrophilic aromatic metalation reactions with compounds of other metals, for example Tl(III), Pb(IV), Sn(IV), Pt(IV), Au(III), Rh(III), and Pd(II), have been discovered [4]. In this chapter, we will focus on intermolecular S_EAr reactions involving main-group metal electrophiles and resulting in the formation of isolable metal aryls which find numerous important applications in synthesis [5]. Well-known electrophilic cyclometalation reactions, for example cyclopalladation can be found in other chapters of this book and will not be reviewed here.

In comparison with other methods used to arylate metals, direct metalation of aromatic C–H bonds is particularly attractive because of its simplicity. Like any S_EAr reaction [6], electrophilic metalation may lead to a mixture of positional isomers, depending on the nature of the substrate, metal reagent, solvent, and reaction conditions. On the other hand, electrophilic metalation is a cost-efficient process which provides useful organometallic compounds directly from arenes and inexpensive inorganic precursors. Alternative methods employ more costly functionalized aromatic compounds (e.g. haloarenes), active organometallic reagents (e.g. aryl lithiums and Grignard reagents), and purified dry solvents. Unlike C–H activation via oxidative addition to electron-rich derivatives of metals in low oxidation states, electrophilic metalation always involves metals in high oxidation states.

1.2.2.2 **Mercuration**

Aromatic mercuration (Scheme 1), the oldest S_EAr metalation reaction known, has been the subject of several reviews and monographs [7–11].



Scheme 1. Mercuration of a substituted benzene.

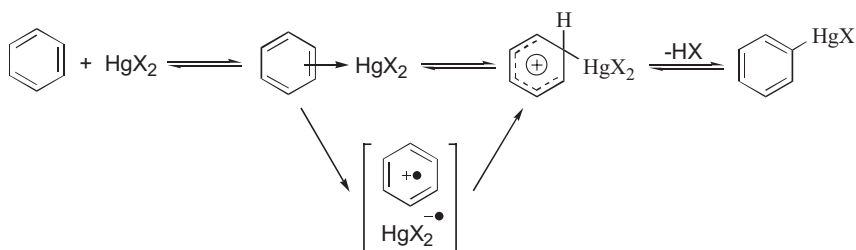
Numerous studies have revealed an electrophilic mechanism of aromatic mercuration. For example, the reactivity of a mercurating agent HgX_2 strongly

depends on the nature of the counter-ion X . Weaker anionic donors X result in enhanced electrophilicity of the mercury center. Thus, mercuric cyanide and halides have proven to be unreactive (or barely reactive), whereas $Hg(II)$ acetate has greater electrophilic character and hence is more often used to mercurate aromatics. In the presence of ionizing $HClO_4$, aromatic mercuration with $Hg(OAc)_2$ occurs even faster [7]. Furthermore, mercury trifluoroacetate (TFA) in trifluoroacetic acid (TFAH) is a remarkably powerful reagent which mercurates benzene 6.9×10^5 times faster than $Hg(OAc)_2$ in acetic acid [12]. Up to five Hg atoms can be introduced into the benzene ring with $Hg(TFA)_2$ [13], whereas use of $Hg(OAc)_2$ leads to the mono- and dimercurated products only. Icosahedral closo-carboranes $C_2B_{10}H_{12}$ seem unreactive toward $Hg(OAc)_2$ but undergo smooth mercuration with $Hg(TFA)_2$ in TFAH [14].

Kinetic experiments have demonstrated that the mercuration of benzene with mercury acetate or nitrate is second order, first order in each of the mercury salt and the arene [7]. Electron-donating substituents on the ring increase mercuration rates, whereas electron-withdrawing groups slow down the reaction [7–11]. For example, mercuration of nitrobenzene requires $150^\circ C$ to occur and reaction of benzene with $Hg(OAc)_2$ in $AcOH$ takes hours at 90 – $120^\circ C$ whereas N,N -dimethylaniline readily reacts with $Hg(OAc)_2$ in aqueous $EtOH$ at room temperature within a few minutes [7].

The mechanism of mercuration is shown in Scheme 2. In the first step, the mercury salt forms a π -complex with the aromatic substrate [15, 16]. In 1982, Lau, Huffman, and Kochi [17] reported the first isolation and full characterization (including X-ray molecular and crystal structure) of such an intermediate, a complex of hexamethylbenzene with $Hg(TFA)_2$. The X-ray structure revealed a $Hg_2(\mu-TFA)_4$ framework with a molecule of C_6Me_6 η^2 -coordinated to each of the Hg atoms. Analogous π -complexes have also been observed and studied by Dean and co-workers [18] and more recently by Barron's [19] and Gabbai's [20] groups. The π -complex intermediate can rearrange to the σ -complex (a Wheland intermediate) directly, or sometimes via electron transfer, to produce a radical ion pair which then collapses (Scheme 2) [21,22].

Hundreds of reports have been published on electrophilic mercuration of a variety of aromatic compounds and uses of the resulting organomercurials in synthesis [5, 7–11]. Although in this chapter, we will not discuss synthetic applica-

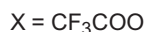
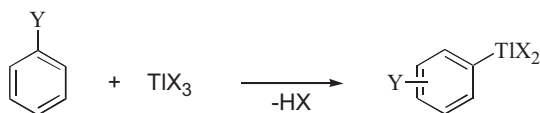


Scheme 2. Mechanism of electrophilic aromatic mercuration.

tions of aromatic mercuration, because of space limitations, one interesting recent example is noteworthy. Buzhansky and Feit [23] have reported the synthesis of optoelectronic-relevant unsubstituted oligo(α -thiophenes) by one-pot mercuration of thiophene with $\text{Hg}(\text{TFA})_2$ then homocoupling of the resulting organomercurial with $\text{PdCl}_2/\text{Et}_3\text{N}$. The procedure can then be repeated with the 2,2'-bithienyl produced to give a tetramer which, in turn, can be further dimerized in the same manner. The yields for the individual isolated oligomers were in the range of 70–92 % [23].

1.2.2.3 Thallation

The earliest examples of direct aromatic thallation, reported by Gilman and Abbott [24] and Glushkova and Kocheshkov [25], employed weak thallium electrophiles TlCl_3 and $\text{Tl}(i\text{-PrCO}_2)_3$, respectively. It was not until the late 1960s and early 1970s that Taylor, McKillop and co-workers [26] prepared thallium(III) trifluoroacetate, $\text{Tl}(\text{TFA})_3$, and demonstrated its utility as a potent electrophile for aromatic thallation (Scheme 3). Several reviews have been published on thallium(III) aryls [27–30]; the paper by Usyatinskii and Bregadze [29] provides particularly comprehensive coverage of the thallation reaction and its applications in synthesis.



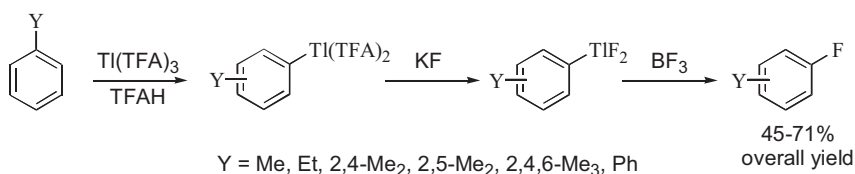
Scheme 3. Thallation of a substituted benzene with $\text{Tl}(\text{TFA})_3$.

In general, Tl^{3+} seems to be a weaker electrophile than Hg^{2+} ; as a result, the rate of thallation is a factor of approximately 200–400 times slower than the rate of mercuration under similar conditions [29]. Electron-enriched arenes such as alkylbenzenes undergo thallation with $\text{Tl}(\text{TFA})_3$ in TFAH within minutes at room temperature. Slightly deactivated aromatic rings ($\text{Y} = \text{halide}$ in Scheme 3) can be thallated in less than an hour in TFAH under reflux, but with less nucleophilic arenes (e.g. $\text{Y} = \text{CF}_3$) the reaction takes days to go to completion. Being bulkier and less electrophilic, $\text{Tl}(\text{TFA})_3$ metalates substituted benzenes with higher positional selectivity than $\text{Hg}(\text{TFA})_2$. For example, the thallation of monoalkylbenzenes is much more para-selective than the mercuration. Remarkably, however, some substituents Y containing a donor atom direct the thallation in the ortho position with uncommonly high efficiency [26]. For example, benzoic acid is thallated with $\text{Tl}(\text{TFA})_3$ in TFAH to give the ortho derivative with 95 % selectivity, the other 5 % being the expected meta isomer [26]. Benzyl alcohol undergoes the thallation exclusively in the ortho position. This unusual ortho selectivity is explained by the original coordination of the donating heteroatom of Y to Tl^{3+} , followed by intramo-

molecular electrophilic substitution of the ortho H. Such “chelate intermediates” are stable and therefore operative only for 5- or 6-membered rings, otherwise the ortho selectivity is decreased considerably or lost altogether. Indeed, the ortho selectivity of thallation of a series of $\text{Ph}(\text{CH}_2)_n\text{COOH}$ was found to be 95, 92, 29, 6, and 5 % for $n=0, 1, 2, 3$, and 4, respectively [26]. Also, being a reversible process, electrophilic aromatic thallation can lead to mixtures of positional isomers in different ratios depending on reaction temperature and time (kinetic vs. thermodynamic control) [26, 29].

The electrophilic thallation path involves $[\text{Tl}(\text{TFA})_2]^+$ as the active electrophile which forms a π -complex with the substrate [16, 31]. Single electron transfer from electron-enriched polymethylarenes can be significant, leading to the formation of biaryls and side-chain thallated products [31]. The electron transfer path during electrophilic metalation is much more characteristic of $\text{Tl}(\text{TFA})_3$ than $\text{Hg}(\text{TFA})_2$ [16]. A review article [29] includes useful analysis of mechanistic features of aromatic thallation with $\text{Tl}(\text{TFA})_3$ and some other $\text{Tl}(\text{III})$ reagents, including the even more electrophilic triflate.

Once introduced into the aromatic ring, the TlX_2 functionality can be displaced with a variety of groups such as halides, CN, SCN, SeCN, NO_2 , and SO_2Ar . These reactions and their possible mechanisms have been extensively reviewed [27–30]. In this chapter, we will mention only one such reaction [32] furnishing valuable fluoroarenes and thus providing a rare alternative [33] to the Balz–Schiemann reaction – the synthesis of ArF via the thermal decomposition of arenediazonium tetrafluoroborates or hexafluorophosphates. The method (Scheme 4) is limited to electron-rich arenes only. Arylthallium fluorides containing no electron-donating groups on the ring produce only trace quantities of the desired aryl fluorides [32].

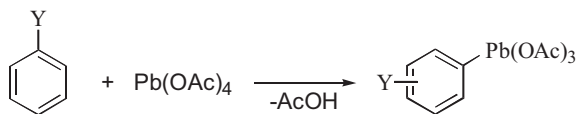


Scheme 4. Synthesis of fluoroarenes via electrophilic thallation.

1.2.2.4 Plumbylation (Plumbation)

In recent years, there has been much interest in the use of aryllead compounds in organic synthesis, because of the ability of compounds of the type $\text{ArPb}(\text{O}_2\text{CR})_3$ to smoothly arylate a variety of nucleophiles [34–37]. Aryllead tricarboxylates can be prepared by direct plumbylation of aromatic compounds (Scheme 5), a reaction that has been known for a long time [38].

Lead(IV) acetate is most commonly employed to plumbylate arenes, often using chloroform as the solvent. Being a relatively weak electrophile, $\text{Pb}(\text{OAc})_4$ can react only with electron-rich aromatic compounds, for example anisole and polyalkoxybenzenes. The electrophilicity of the lead reagent is, however, enhanced substan-

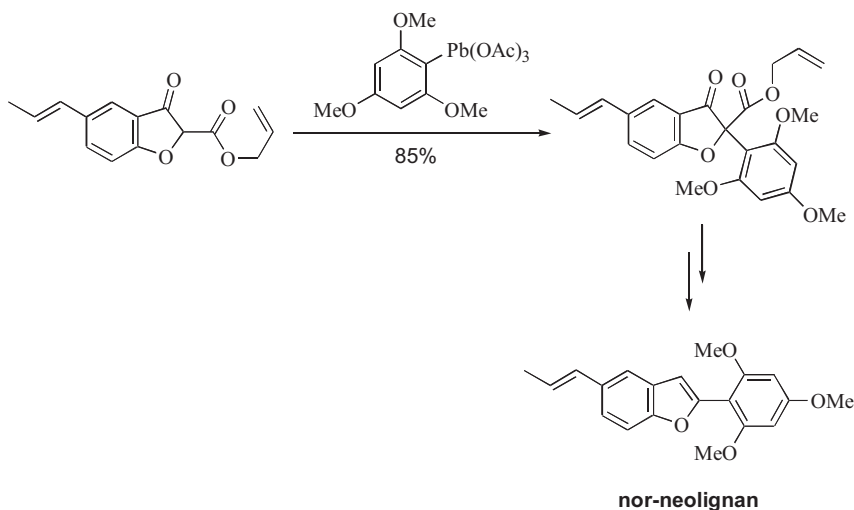


Scheme 5. Plumbylation of a substituted benzene with lead(IV) acetate.

tially in the presence of acetic acid and especially its polychlorinated derivatives [37]. Although anisole is poorly reactive toward $\text{Pb}(\text{OAc})_4$ in benzene, the reaction is efficient in AcOH [39] and even faster in dichloroacetic acid [37]. At room temperature, toluene is readily plumbylated with $\text{Pb}(\text{OAc})_4$ in Cl_2CHCOOH [40] or Cl_3CCOOH [37] but not in AcOH .

Lead(IV) trifluoroacetate in TFAH is a very reactive electrophile that is capable of plumbylating less electron-rich arenes. Nonetheless, the use of trifluoroacetate anions in the plumbylation reactions should be avoided, because aryllead(IV) trifluoroacetates are unstable compounds that readily decompose to the corresponding aryl trifluoroacetates and biaryls [34–37, 40, 41]. It has been reported [41] that $4\text{-FC}_6\text{H}_4\text{ArPb}(\text{TFA})_3$ is reasonably stable and can be isolated from the reaction of $\text{Pb}(\text{TFA})_4/\text{TFAH}$ with fluorobenzene. A mechanistic study [41] indicated an electrophilic substitution path for the plumbylation reaction, which seemed to be substantially more para-selective than mercuration and thallation. For example, the plumbylation of toluene with $\text{Pb}(\text{OAc})_4$ in dichloroacetic acid has been reported [41] to occur with >90 % para-selectivity.

The products of direct aromatic plumbylation, $\text{ArPb}(\text{OAc})_3$, are attractive reagents, because of their accessibility and ability to arylate various nucleophiles under mild conditions [36]. These arylation reactions might involve ligand exchange at the $\text{Pb}(\text{IV})$ center, followed by reductive elimination [35]. Among nu-

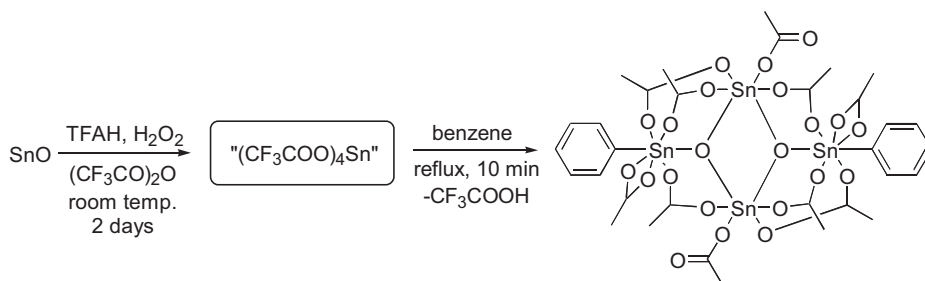


Scheme 6. Arylation with an organolead compound as a key step in the synthesis of nor-neolignan.

merous applications of aryllead(IV) carboxylates is the formation of a quaternary carbon center on C-arylation; this is particularly valuable for natural product synthesis [36]. This type of reaction can be exemplified by the synthesis of nor-neolignan, involving an aryllead reagent in a key step (Scheme 6) [42].

1.2.2.5 Stannylation

Discovered by Thorn and first communicated only a few years ago [43], electrophilic aromatic stannylation is the newest of all metalation reactions described in this chapter. The reactive Sn electrophile can be prepared by dearylation of Ph_4Sn with TFAH or, preferably, by reaction of SnO with trifluoroperacetic acid generated from H_2O_2 , TFAH, and trifluoroacetic anhydride. Because the structure of the Sn(IV) species (or mixtures of species) produced this way is unknown, the reactive electrophile is depicted as “ Sn(TFA)_4 ”, for simplicity. The stannylation reactions of benzene and *p*-xylene were shown to produce tetratin clusters containing two “inorganic” and two “organometallic” Sn centers (Scheme 7).



Scheme 7. Electrophilic stannylation of benzene.

The structures of both the phenyl and 2,5-dimethylphenyl tin clusters were established by single-crystal X-ray diffraction. Under similar conditions, toluene was stannylated to produce a mixture of organotin compounds. Bromination of this mixture yielded 3-bromotoluene and 4-bromotoluene in a 2:1 ratio, with trace amounts of 2-bromotoluene. Similarly, PhBr was produced upon treatment of the phenyltin product with aqueous Br_2 . No applications of the stannylation reactions have yet been reported.

Experimental

Mercuration of *N,N*-dimethylaniline [2, 7, 44, 45]

Solutions of Hg(OAc)_2 (60 g) in 50 % EtOH (400 mL) and *N,N*-dimethylaniline (50 g) in 96 % EtOH are poured together. The initially clear mixture thickens after a few minutes into a mash of fine needles of *p*-dimethylaminophenylmercury acetate, m.p. 165 °C (from EtOH). The product was isolated in 94 % yield when half the amount of the mercuric acetate solution was used under similar conditions [44]. The compound has been characterized by X-ray diffraction, analysis,

and spectroscopy (NMR, IR, ES-MS) data [45]: Anal. Calcd. for $C_{10}H_{13}NO_2Hg$, %: C, 31.62; H, 3.45; N, 3.67. Found, %: C, 31.76; H, 3.38; N 3.58. 1H NMR ($CDCl_3$): δ = 2.08 (s, CCH_3), 2.95 (s, NCH_3), 7.12, 6.69 (two d, J = 8.8 Hz, H_{aryl}); ^{13}C NMR δ = 23.5 (CCH_3), 40.3 (NCH_3), 113.0 (C3, $^3J_{C-Hg}$ = 212 Hz), 128.5 (C1), 136.8 (C2, $^2J_{C-Hg}$ = 142 Hz), 151.0 (C4), 177.5 (C=O); ^{199}Hg NMR δ = 930. ES-MS (MeOH, HPF_6) m/z 382 $[M + H]^+$. IR (KBr, cm^{-1}) 945 m, 926 m, 803 vs, 794 sh, 752 w, 690 s, 650 w, 614 w, 570 w, 509 m, 476 w.

***o*-Iodophenylacetic acid via thallation of phenylacetic acid [26]**

A vigorously stirred suspension of 50 g of thallium(III) oxide in 200 mL TFAH containing 25 mL water was heated under reflux for 12 h in a flask wrapped with aluminum foil. Filtration of the cooled reaction mixture to remove a small amount of residual solid then gave an approximately 0.88 M solution of $Tl(TFA)_3$ in TFAH. Evaporation of the TFAH from the colorless solution under reduced pressure gave $Tl(TFA)_3$ as a granular solid in 90–100 % yield. A solution of 2.72 g (0.02 mol) phenylacetic acid in 20 mL of a 1 M solution of $Tl(TFA)_3$ in TFAH was stirred for 48 h at room temperature. The reaction mixture was suspended in 100 mL water and KI (8 g, 0.05 mol) was added. The suspension was heated under reflux for 5 h, and sodium metabisulfite (1 g) was then added to reduce iodine that had been formed during the reaction. Heating was continued for another 30 min, and the precipitated thallium(I) iodide was removed by filtration (without prior cooling). The collected inorganic material was thoroughly washed with acetone. The combined filtrate and acetone washings were extracted with ether (3×40 mL), and the ether extracts were dried over anhydrous sodium sulfate and evaporated to give crude *o*-iodophenylacetic acid (5.10 g, 97.5 %), m.p. 80–90 °C. Recrystallization from petroleum ether gave 3.80 g purified acid, m.p. 108–110 °C. Methylation of a small sample with diazomethane and subsequent inspection of the resulting methyl ester by GC showed the compound to be pure methyl *o*-iodophenylacetate.

Plumbylation of 1,3,5-trimethoxybenzene [37]

A solution of 1,3,5-trimethoxybenzene (10.03 g, 0.06 mol) in dry $CHCl_3$ (20 mL) was added dropwise over 15 min to a well-stirred solution of $Pb(OAc)_3$ (10.00 g, 0.022 mol) in dry $CHCl_3$ (75 mL) at room temperature and the mixture was stirred for 8 h. The mixture was washed with H_2O (3×100 mL), the organic phase dried, concentrated to 20 mL, and added dropwise to light petroleum ether (500 mL), whereupon a bright yellow solid precipitated. This solid was collected by suction filtration and dried to give tris(acetoxy)(2,4,6-trimethoxy)plumbane as yellow plates, yield 8.25 g (68 %); m.p. 175–179 °C (dec).

Stannylation of Benzene [43]

Aqueous H_2O_2 (30 %; 0.40 mL) was slowly added (*Caution: exothermic reaction*) dropwise to a vigorously stirred mixture of SnO (0.50 g), TFAH (3 mL), and trifluoroacetic anhydride (4 mL). This mixture was stirred at room temperature for 2 days until the dark solids (SnO) had all dissolved. The resulting white opaque solution was evaporated under N_2 and the residue was treated first with trifluoro-

acetic anhydride (6 mL) and then with a solution of trifluoroacetic acid freshly prepared by slowly adding 0.63 mL 30 % H_2O_2 to $(\text{CF}_3\text{CO})_2\text{O}$ (10 mL; *Caution: exothermic reaction*) at 0–5 °C. The mixture was stirred at room temperature for 30 h, filtered through glass-wool under N_2 , and reduced in volume to ca. 2–4 mL. Dry CH_2Cl_2 (30 mL) then hexane (5 mL) were added, and the mixture was stirred until the originally precipitated oil solidified. The solid was separated, washed with hexane, and dried under vacuum. The yield of “ $\text{Sn}(\text{TFA})_4$ ” (see above) was 0.69 g. To this solid, was added dry benzene (6 mL) and the mixture was stirred under reflux (N_2) for 10 min. Most of the solids dissolved to give a pale pinkish-tan solution which was separated warm from a small amount of viscous oil and left at room temperature. After 2 days white crystalline material precipitated. This was washed with hexane and dried under vacuum. The yield was 0.39 g. X-Ray analysis of one of the crystals found in the solid product indicated the structure shown in Scheme 7. ^1H NMR (CD_2Cl_2 , 20 °C), δ = 7.7 (m, 3H, *m,p*- C_6H_5); 7.9 (m, 2H, $J_{\text{Sn-H}}$ = 177 Hz, *o*- C_6H_5). A weak singlet at 7.4 ppm from benzene was also observed. ^{19}F NMR (CD_2Cl_2 , 20 °C), δ = 75.7 (s). To determine the amount of phenyltin species in this product, 301 mg of it was treated, in CDCl_3 (2 mL), with excess aqueous bromine (4 mL). After 1 h vigorous stirring at room temperature all the solids had dissolved. ^1H NMR analysis of the organic phase with 1,2-dichloroethane as internal standard indicated the presence of bromobenzene (48 mg), benzene (8 mg) and no other products. The amount of bromobenzene produced translated into 91 % purity of $[(\text{Ph})_2\text{Sn}_4\text{O}_2(\text{TFA})_{10}]$, under the cautious assumption that this was the only Ph-Sn species formed in the stannylation reaction.

1.2.3

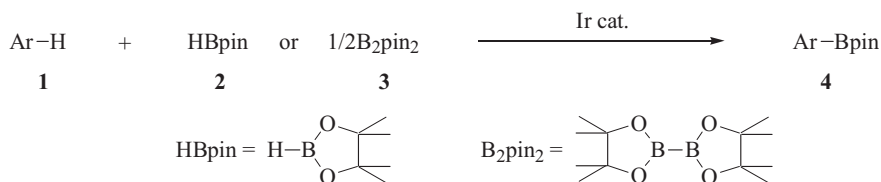
Iridium-Catalyzed Borylation of Arenes

Tatsuo Ishiyama and Norio Miyaura

1.2.3.1 Introduction and Fundamental Examples

Aromatic boron derivatives are an important class of compound the utility of which has been amply demonstrated in various fields of chemistry. Traditional methods for their synthesis are based on the reactions of trialkylborates with aromatic lithium or magnesium reagents derived from aromatic halides. Pd-catalyzed cross-coupling of aromatic halides with tetra(alkoxo)diborons or di(alkoxo)-boranes is a milder variant in which the preparation of magnesium and lithium reagents is avoided. Alternatively, transition metal-catalyzed aromatic C–H borylation of aromatic compounds **1** by pinacolborane (HBpin, pin = $\text{O}_2\text{C}_2\text{Me}_4$) **2** or bis(pinacolato)diboron **3** [1, 2], which was first reported in 1999 [3], is highly attractive as a convenient, economical, and environmentally benign process for synthesis of aromatic boron compounds **4** without any halogenated reactant. Among the catalysts developed to date, an Ir system has excellent activity and selectivity for the aromatic C–H borylation (Scheme 1).

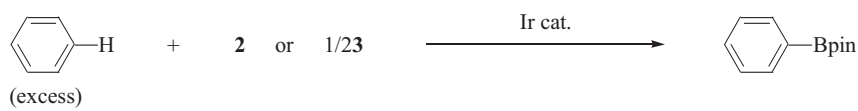
Aromatic C–H borylation is catalyzed by an Ir complex with a small and electron-donating ligand, for example PMe_3 , 1,2-bis(dimethylphosphino)ethane (dmpe), 2,2'-bipyridine (bpy), and 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbpy) (Table 1)



Scheme 1. Iridium-catalyzed aromatic C–H borylation.

[3–10]. The maximum turnover number achieved in the reaction of benzene with **2** is 4500 when using $\text{Ir}(\eta^5\text{-C}_9\text{H}_7)(\text{cod})\text{-dmpe}$ at 150 °C; for reaction with **3** the TON is 8000 when using $1/2[\text{IrCl}(\text{coe})_2]_2\text{-dtbpy}$ at 100 °C. The bpy-based Ir catalysts are effective for borylation by either **2** or **3** at lower temperature. $1/2[\text{IrCl}(\text{coe})_2]_2\text{-dtbpy}$ catalyzes the reaction even at room temperature.

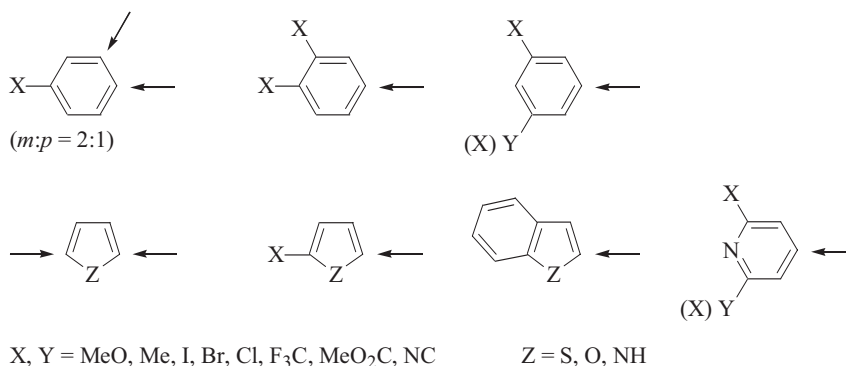
Table 1. Representative catalysts and their activity.



Reagent	Ir cat.	Temp. (°C)	Time (h)	Yield (%)	TON
2	$\text{Ir}(\eta^5\text{-C}_9\text{H}_7)(\text{cod})\text{-2PMe}_3$ (2.0 mol%)	150	18	88	–
2	$\text{Ir}(\eta^5\text{-C}_9\text{H}_7)(\text{cod})\text{-dmpe}$ (0.02 mol%)	150	61	90	4500
2	$1/2[\text{IrCl}(\text{cod})]_2\text{-bpy}$ (3.0 mol%)	80	16	80	–
3	$1/2[\text{IrCl}(\text{cod})]_2\text{-bpy}$ (1.5 mol%)	80	16	95	–
3	$1/2[\text{IrCl}(\text{coe})_2]_2\text{-dtbpy}$ (0.01 mol%)	100	16	80	8000
3	$1/2[\text{IrCl}(\text{coe})_2]_2\text{-dtbpy}$ (2.5 mol%)	25	4.5	83	–

$\text{dmpe} = \text{Me}_2\text{P}-\text{CH}_2\text{CH}_2-\text{PMe}_2$
 $\text{bpy} = \text{pyridine-2,2'-diyl}$
 $\text{dtbpy} = \text{4,4'-di-}t\text{-butylpyridine-2,2'-diyl}$

Functional group tolerance of the borylation is quite high. The reaction occurs selectively at the C–H bond for **1** bearing MeO, Me, I, Br, Cl, F_3C , MeO_2C , and NC groups (Scheme 2) [4–10]. In particular, it is interesting to note that aromatic C–H bonds are selectively borylated even in the presence of weaker benzylic C–H bonds or C-halogen bonds.



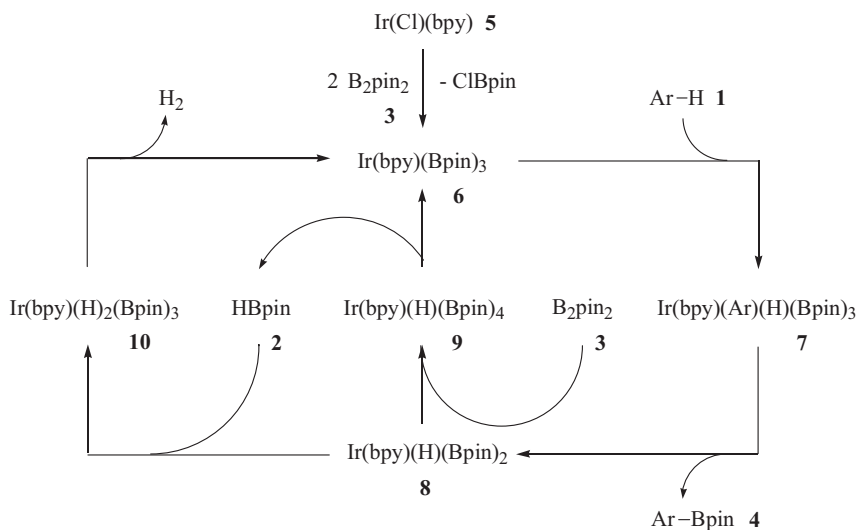
Scheme 2. Functional group tolerance and regiochemistry.

Regiochemistry of the borylation is summarized in Scheme 2. For arenes, regiochemistry is primarily controlled by the steric effects of substituents [4–6, 8, 10]. Both electron-rich and electron-poor monosubstituted arenes produce regioisomeric mixtures of meta and para borylation products in statistical ratios (ca. 2:1) indicating no significant electronic influence of substituents on regioselectivity. Thus, 1,2-disubstituted arenes bearing identical substituents yield **4** as single isomers. The borylation of 1,3-disubstituted arenes proceeds at the common meta position; therefore, regioisomerically pure **4** are obtained even for two distinct substituents on the arenes. In the case of five-membered heteroarenes, the electronegative heteroatom causes the α -C–H bonds to be active for the borylation [7–10]. Unsubstituted substrates yield mixtures of 2-borylated and 2,5-diborylated products, but both products are selectively obtained by reactions with the appropriate ratio of substrate and reagent. On the other hand, monoborylation selectively occurs for 2-substituted or benzo-fused substrates. For pyridines 2,6-disubstituted substrates undergo smooth borylation at the γ -position [5], whereas pyridine itself is significantly less reactive, because of the strong coordinating ability of the basic nitrogen for the catalyst [7].

1.2.3.2 Mechanism

The mechanism proposed for aromatic C–H borylation of aromatic compounds **1** by B₂pin₂ **3** catalyzed by the Ir-bpy complex is depicted in Scheme 3 [6–9]. A tris(boryl)Ir(III) species [5, 6, 11] **6** generated by reaction of an Ir(I) complex **5** with **3** is chemically and kinetically suitable to be an intermediate in the catalytic process. Oxidative addition of **1** to **6** yields an Ir(V) species **7** that reductively eliminates an aromatic boron compound **4** to give a bis(boryl)Ir(III) hydride complex **8**. Oxidative addition of **3** to **8** can be followed by reductive elimination of HBpin **2** from **9** to regenerate **6**. **2** also participates in the catalytic cycle via a sequence of oxidative addition to **8** and reductive elimination of H₂ from an 18-electron Ir(V) intermediate **10**. Borylation of **1** by **2** may occur after consumption of **3**, because the catalytic reaction is a two-step process – fast borylation by **3** then slow borylation by **2** [6].

Catalytic borylation by **2** may proceed through intermediates **6**, **7**, **8**, and **10**, in which **6** can be generated by the reaction of **5** with **2** [10]. A similar process is also postulated for the borylation of **1** by **2** catalyzed by phosphine-based Ir complexes [5]. Although the possibility of an Ir(I)–Ir(III) cycle cannot be completely eliminated, the synthetic [4–10], mechanistic [5, 6], and theoretical studies [12] support the Ir(III)–Ir(V) cycle.

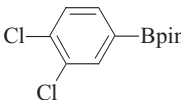
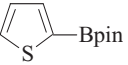
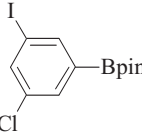
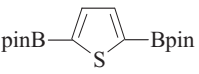
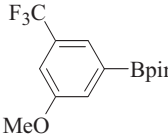
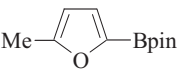
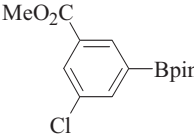
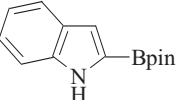
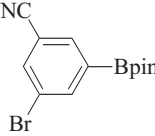
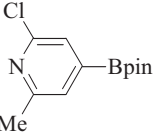


Scheme 3. Proposed mechanism for borylation by B_2pin_2 **3**.

1.2.3.3 Scope and Limitations

Although C–H borylation of aromatic compounds **1** by HBpin **2** or B_2pin_2 **3** is usually performed using an excess of substrate or reagent at high temperature, reactions at room temperature with stoichiometric amounts of **1** toward **2** or **3** in an inert solvent is desirable for thermally unstable, expensive, or solid substrates. It has recently been reported that an Ir complex comprised of $1/2[\text{Ir}(\text{OMe})(\text{cod})]_2$ and dtbpy is a highly active catalyst for the aromatic C–H borylation by **2** or **3**. This high activity enables room-temperature borylation of **1** by **2** or **3** with a stoichiometric amount of **1** toward **2** or **3** in hexane to produce the corresponding aromatic boron compounds **4** in high yields with high regioselectivity. With this advance, the aromatic C–H borylation provides a practical tool for preparing **4**. Representative examples are shown in Table 2 [8–10].

Table 2. Stoichiometric borylation of aromatic compounds **1** by HBpin **2** or B₂pin₂ **3** catalyzed by 1/2[Ir(OMe)(cod)]₂-dtbpy in hexane at room temperature; a: 5 equiv. of **1** to **2**, b: 10 equiv. of **1** to **3**, c: 0.45 equiv. of **1** to **2**, d: 1 equiv. of **1** to **3**.

Product	Yield (%)		Product	Yield (%)	
	2	3		2	3
	73 (8 h)	82 (8 h)		75 ^a (0.5 h)	91 ^b (1 h)
	67 (8 h)	82 (4 h)		86 ^c (2 h)	83 ^d (0.5 h)
	73 (24 h)	81 (8 h)		83 (2 h)	85 (2 h)
	70 (24 h)	80 (8 h)		99 (0.5 h)	88 (0.5 h)
	74 (2 h)	83 (2 h)		75 (2 h)	84 (4 h)

Experimental

3-Bromo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile

A 25-mL flask containing a magnetic stirring bar and assembled with a septum inlet, a condenser, and a bubbler was charged with [Ir(OMe)(cod)]₂[13] (0.015 mmol) and 4,4'-di-*tert*-butyl-2,2'-bipyridine (0.03 mmol), and then flushed with nitrogen. Dry hexane (6 mL), pinacolborane (1.1 mmol), and 3-bromobenzonitrile (1.0 mmol) were added, and the mixture was stirred at 25 °C for 2 h. The reaction mixture was treated with water at room temperature, extracted with ben-

zene, washed with brine, and dried over MgSO_4 . Kugelrohr distillation in vacuo gave an analytically pure sample. The purity, determined by NMR and GC analysis was, >95%; ^1H NMR (CDCl_3 , 400 MHz) δ 1.35 (s, 12 H), 7.85 (s, 1 H), 8.01 (s, 1 H), 8.13 (s, 1 H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 24.81, 84.85, 113.77, 117.32, 122.60, 136.70, 136.74, 141.73; exact mass calcd for $\text{C}_{13}\text{H}_{15}\text{BBrNO}_2$ 307.0379, found 307.0387.

2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)indole

A 25-mL flask containing a magnetic stirring bar and assembled with a septum inlet, a condenser, and a bubbler was charged with $[\text{Ir}(\text{OMe})(\text{cod})]_2$ [13] (0.015 mmol), 4,4'-di-*tert*-butyl-2,2'-bipyridine (0.03 mmol), and bis(pinacolato)di-boron (1.0 mmol), and then flushed with nitrogen. Dry hexane (6 mL) and indole (2.0 mmol) were added, and the mixture was stirred at 25 °C for 0.5 h. The reaction mixture was treated with water at room temperature, extracted with benzene, washed with brine, and dried over MgSO_4 . Kugelrohr distillation in vacuo gave an analytically pure sample. The purity determined, by NMR and GC analysis, was >95%; ^1H NMR (CDCl_3 , 400 MHz) δ 1.36 (s, 12 H), 7.09 (t, 1 H, J = 7.7 Hz), 7.11 (s, 1 H), 7.23 (t, 1 H, J = 8.3 Hz), 7.38 (d, 1 H, J = 8.3 Hz), 7.67 (d, 1 H, J = 7.8 Hz), 8.56 (br s, 1 H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 24.78, 84.13, 111.25, 113.83, 119.75, 121.57, 123.59, 128.24, 138.18; exact mass calcd for $\text{C}_{14}\text{H}_{18}\text{BNO}_2$ 243.1431, found 243.1433.

1.2.4

Transition-metal Catalyzed Silylation of Arenes

Fumitoshi Kakiuchi

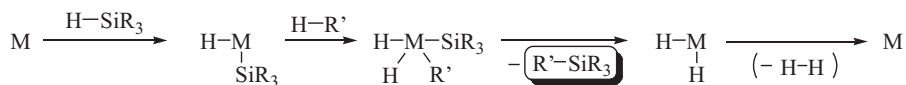
1.2.4.1 Introduction and Fundamentals

Catalytic C–H bond transformation is a very attractive research subject in organic and organometallic chemistry [1]. There are several procedures for C–H bond transformation. One is conversion of C–H bonds to C–Si bonds, i.e. the direct silylation of C–H bonds. Three procedures have been developed for silylation of C–H bonds – use of hydrosilanes (reaction 1 in Scheme 1), disilanes (reaction 2 in Scheme 1), and vinylsilanes (reaction 3 in Scheme 1) as silylating reagents.

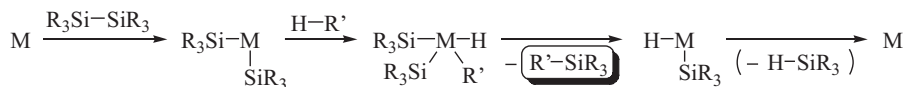
In Scheme 1, reaction 1, two hydrogen atoms remain during the reaction and these should be removed from the metal center to regenerate the low-valent metal species. Generation of molecular hydrogen by reductive elimination is most likely, but this process is usually thermally unfavorable, so the co-presence of an efficient hydrogen acceptor, or use of photoirradiation, is usually required to accomplish the reaction catalytically. In reaction 2, H–M–SiR_3 species should be converted to the low-valent metal by formal dissociation of H–SiR_3 from the metal. In reaction 3 a vinylsilane functions as a silylating reagent and an acceptor of hydrogen. Thus, during the course of the reaction ethylene should be generated. Among these three reactions reaction 1 is the most frequently used in the catalytic silylation of C–H bonds.

For catalytic C–H bond transformation, there are two types of reaction. One involves non-chelation-assisted C–H bond cleavage, the other is chelation-assisted.

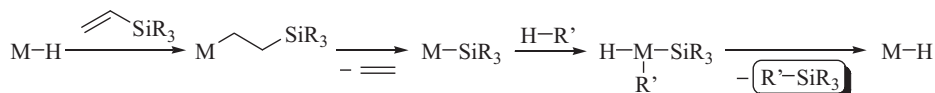
reaction 1



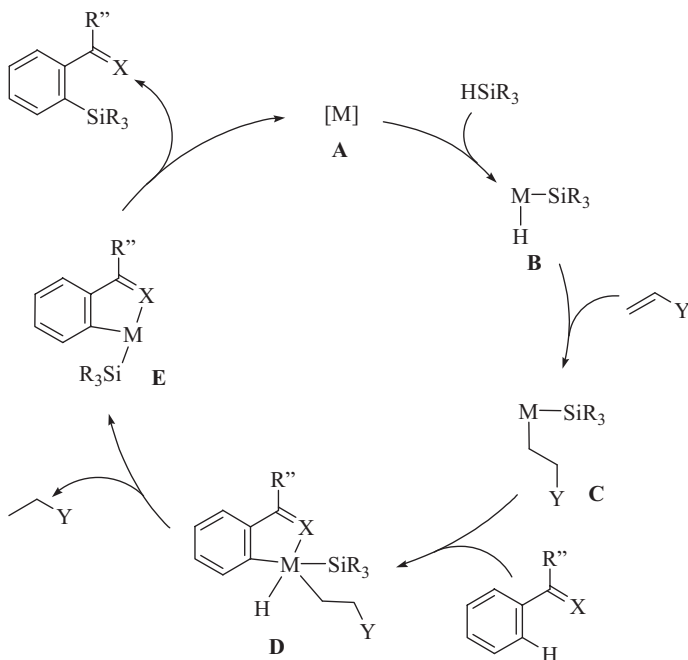
reaction 2



reaction 3

**Scheme 1.** Outlines of reactions for silylation of C-H bonds.

In the former reaction regioisomers are possibly formed, so regioselectivity cannot be controlled. Chelation-assisted reactions, on the other hand, occur regioselectively, usually at the position ortho to the directing group.

**Scheme 2.** One of the possible reaction pathways for the silylation of C-H bonds with hydrosilanes.

1.2.4.2 Mechanism

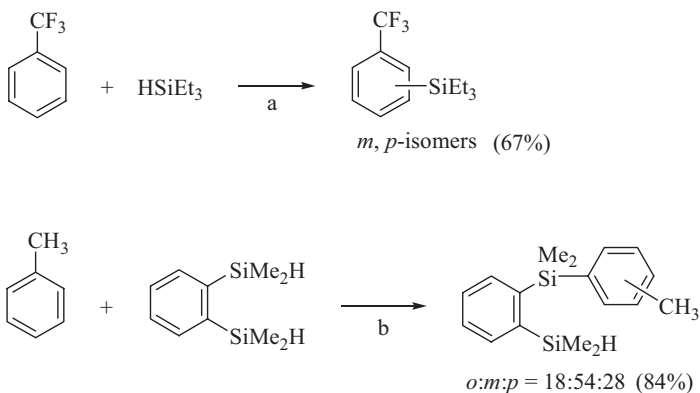
As mentioned above, three types of reaction are used for silylation of C–H bonds. In this section, we describe the reaction pathway of chelation-assisted silylation of C–H bonds with hydrosilanes (reaction 1).

Several reaction pathways for reaction 1 are possible. A clear reaction mechanism has not been elucidated. Although it is premature to discuss the details of the reaction pathway for this silylation reaction, one possible pathway for the chelation-assisted silylation of C–H bonds is shown in Scheme 2. The catalytic reaction is initiated by oxidative addition of hydrosilane to **A**. Intermediate **B** reacts with an olefin to give **C**. Then, addition of a C–H bond to **C** leads to intermediate **D**. Dissociation of alkane from **D** provides Ru(silyl)(aryl) intermediate **E**. Reductive elimination making a C–Si bond gives the silylation product and the active catalyst species **A** is regenerated. Another pathway, addition of a C–H bond to **A** before addition of hydrosilane to **A** is also possible. At present, these two pathways cannot be distinguished.

1.2.4.3 Scope and Limitations

1.2.4.3.1 Silylation with Hydrosilanes

The first example of silylation of C–H bonds in arenes with hydrosilanes was reported by Curtis [2]. Later, silylation of C–H bonds with triethylsilane using a rhodium catalyst was reported (Scheme 3) [3, 4]. The reaction of arenes with bis(hydrosilane) using a platinum catalyst involves a bis(silyl)platinum species in the coupling reaction (Scheme 3) [5]. In these non-chelation-assisted reactions possible regioisomers should be formed.



Scheme 3. Silylation of C–H bonds via non-chelation-assistance: (a) 8 mol% ($\eta^5\text{-C}_5\text{Me}_5$)Rh(H)₂(SiEt₃)₂, *tert*-butylethylene, 150 °C, 250 min; (b) 2 mol% Pt₂(dba)₃, 110 °C, 84 h.

For high regioselectivity, one of the most reliable procedures is chelation-assistance, which involves coordination of a heteroatom to a metal. A representative example of regioselective silylation is the Ru₃(CO)₁₂-catalyzed reaction of aryloxa-

zolines with hydrosilanes in the presence of *tert*-butylethylene as a scavenger of the hydrogen [6]. In this reaction the nitrogen atom in the oxazolyl group functions as a directing group and C–SiR₃ bond formation occurs exclusively at the position ortho to the oxazolyl group (Table 1). For this silylation, triethyl-, dimethylphenyl-, *tert*-butyldimethyl-, and triphenylsilanes have high activity, but hydrosilanes with a heteroatom on the silicon atom have no reactivity. This type of silylation of C–H bonds can be applied to a variety of aromatic compounds with an ester, amide, imino, azo, amino, pyridyl, imidazolyl, pyrazolyl, triazolyl, or tetrazolyl group (Scheme 4) [7, 8]. The directing groups remain intact in the coupling products. The functional group compatibility of this reaction is good. The reaction is tolerant of both electron-donating (Me, OMe, and NMe₂) and electron-withdrawing (CF₃, F, and Cl) groups [8]. Nearly always the corresponding ortho-silylation products are obtained in good to excellent yields. In these reactions the silyl group can be introduced at aromatic C–H bonds (sp² C–H bonds) selectively.

Table 1. Silylations of C–H bonds in aromatic and heteroaromatic compounds and of benzyl C–H bonds; 6 mol% Ru₃(CO)₁₂, HSiEt₃, *tert*-butylethylene or norbornene, toluene, reflux, 20 h.

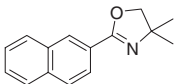
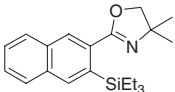
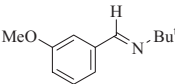
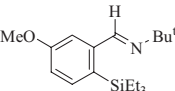
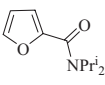
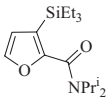
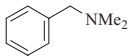
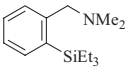
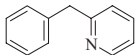
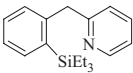
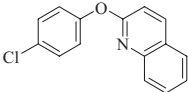
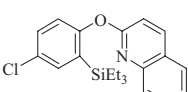
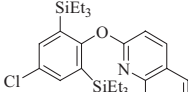
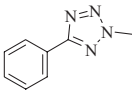
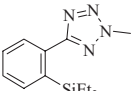
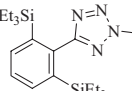


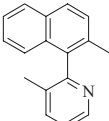
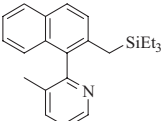
Starting material	Products	Yield (%)	Ref.
		100	5,7
		96	7
		65	7
		58	6
		90	6
6 : 1			

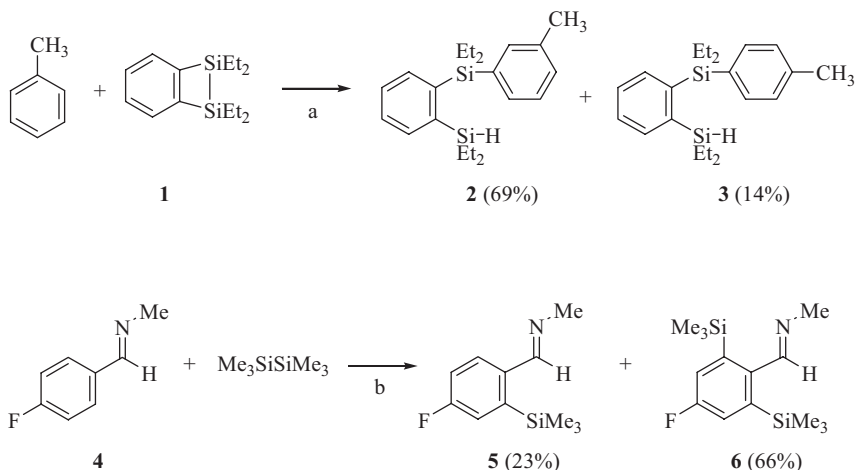
Table 1. Continued

Starting material	Products	Yield (%)	Ref.
	  1 : 1.6	81	6
	  1 : 3	93	7
		78	8
		72	8

Silylation of benzyl C–H bonds using hydrosilanes can also be performed with the aid of $\text{Ru}_3(\text{CO})_{12}$ -catalyst (Table 1) [9]. This silylation occurs only at benzylic CH_3 groups. Pyridine, pyrazole, and hydrazones function as good directing groups. Benzylamines, oxime ethers, dimethylanilides, and aryl pyridyl ethers have no activity in this silylation.

1.2.4.3.2 Silylation with Disilanes

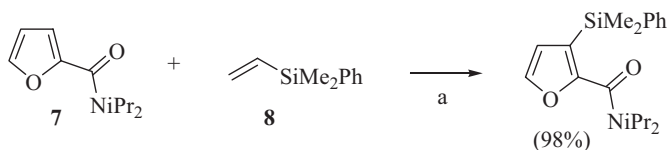
Disilanes are also effective as silylation reagents. Silylation of arenes with strained cyclic disilane **1** occurs with the aid of $\text{Ni}(\text{PEt}_3)_4$ as catalyst [10]. This silylation preferentially occurs at the benzene ring. In the reaction of toluene with disilane **1**, the silylation products **2** and **3** (meta and para isomers) are obtained. A bis(silyl)-nickel intermediate is involved as a key intermediate in this reaction. Platinum(0) complexes have catalytic activity in the silylation of arenes with disilane. Thus, for silylation with disilane, chelation-assistance is also effective for achieving regioselectivity. The silylation with hexaorganodisilanes of aromatic imines **4** with an electron-withdrawing group on the aromatic ring proceeds in the presence of $\text{Pt}_2(\text{dba})_3/\text{P}(\text{OCH}_2)_3\text{Et}$ catalyst to give the silylation products **5** and **6** [11].



Scheme 4. Silylation of C–H bonds with disilanes: (a) 5 mol% $\text{Ni}(\text{PPh}_3)_4$, disilane **1**, toluene, reflux 20 h; (b) 1 mol% $\text{Pt}_2(\text{dba})_3\text{-P}(\text{OCH}_2\text{CH}_3)_3$, toluene, 160 °C, 20 h.

1.2.4.3.3 Silylation with Vinylsilanes

Vinylsilanes can function as a silylating reagents for C–H bonds in heteroaromatic compounds (Scheme 5) [12]. The reaction of furan **7** with vinylsilane **8** using $\text{Ru}_3(\text{CO})_{12}$ as a catalyst affords the β -silylation product in 98 % yield. This silylation can be applied only to heteroaromatic esters, ketones, and amides. For this reaction, $\text{RuHCl}(\text{CO})(\text{PPh}_3)_3$ also has catalytic activity.



Scheme 5. Silylation of C–H bonds with vinylsilanes: (a) 6 mol% $\text{Ru}_3(\text{CO})_{12}$, toluene, 115 °C, 20 h.

Experimental

4,4-Dimethyl-2-(2-methyl-6-triethylsilylanylphenyl)-4,5-dihydrooxazole

$\text{Ru}_3(\text{CO})_{12}$ (38.4 mg, 0.06 mmol), toluene (0.5 mL), 4,4-dimethyl-2-(2-methylphenyl)-4,5-dihydrooxazole (189 mg, 1 mmol), triethylsilane (581 mg, 5 mmol), and 3,3-dimethyl-1-butene (421 mg, 5 mmol) are placed in a 10-mL two-necked flask equipped with a reflux condenser connected to a nitrogen line, a rubber septum, and a magnetic stirring bar, all previously flame-dried under a flow of nitrogen. The resulting solution is heated under reflux under a nitrogen atmosphere for

20 h. The reaction mixture is evaporated to remove volatile materials. TLC (silica gel, hexane–ethyl acetate, 20:1) R_F = 0.30. The product (R_F = 0.30) is isolated by silica gel column chromatography (Merck silica gel 60, 230–400 mesh; column 50 mm i.d. \times 80 mm length; eluent, hexane–ethyl acetate, 10:1): 210 mg (73 % isolated yield; 93 % GC yield). ^1H NMR (CDCl_3) 0.81–0.97 (m, 15 H, CH_2CH_3), 1.43 (s, 6 H, CH_3), 2.35 (s, 3 H, ArCH_3), 4.11 (s, 2 H, CH_2), 7.19 (d, J = 7.16 Hz, 1 H, ArH), 7.26 (dd, J = 7.29 Hz, 7.16 Hz, 1 H, ArH), 7.35 (dd, J = 7.29 Hz, 1.35 Hz, 1 H, ArH); ^{13}C NMR (CDCl_3) 3.86 (SiCH_2), 7.55 (CH_2CH_3), 19.92 (ArCH_3), 28.68 (CH_3), 68.20 ($\text{C}(\text{CH}_3)_2$), 78.73 (CH_2), 128.32, 130.66, 132.85, 134.82, 135.72, 136.74 (Ar), 163.07 ($\text{C}=\text{N}$).

1.3

Alkylation and Vinylation of Arenes

1.3.1

Friedel–Crafts-type Reactions

1.3.1.1 Comparison of Classical and Fancy Catalysts in Friedel–Crafts-type Reactions

Gerald Dyker

1.3.1.1.1 Introduction and Fundamental Examples

Friedel–Crafts alkylations and acylations are still among the most important C–C-coupling reactions (also see next Chapter, 1.3.1.2). Besides the classical Friedel–Crafts catalysts – Bronstedt and Lewis acids – related transition metal-catalyzed methods have emerged in recent years featuring outstanding regio- or even stereoselectivity. Because some of these new methods are assumed to proceed via an initial metalation step at the arene rather than by an activation of the electrophile, they are not usually published under the label “Friedel–Crafts reaction”, although with in respect of the product formed they could not be distinguished. For example, for the AuCl_3 -catalyzed reaction of 2-methylfuran (**1**) with methyl vinyl ketone (**2**, MVK) at least two mechanistic pathways must be discussed [1], a Michael-type process with a metalation of the furan **1** as the first step and a conjugate addition reaction as a second step. According to NMR studies AuCl_3 indeed interacts with furan **1**. Alternatively a Friedel–Crafts-type process might have occurred, either directly with AuCl_3 as Lewis-acidic catalyst or with Bronstedt-acidic catalysts $\text{H}[\text{AuCl}_3\text{OH}]$, $\text{H}[\text{AuCl}_4]$ or even hydrochloric acid as hydrolysis product.

The uncertainty about the active catalyst prompted us to test a variety of classical acidic catalysts in comparison with gold(III)chloride in coupling reactions of arenes with MVK **2**. As a second model reaction we chose the propargylation of arenes with propargylic alcohols. Of course these studies might not answer the mechanistic questions, but they are certainly of practical value.



2

3 (80-90 %)

native catalysts for the reaction depicted in Scheme 1, but both acids proved much less effective than AuCl_3 . HCl , especially, is uneconomical, because of the competing addition reaction forming 4-chlorobutan-2-one as byproduct. Nevertheless,



2 (excess)



6



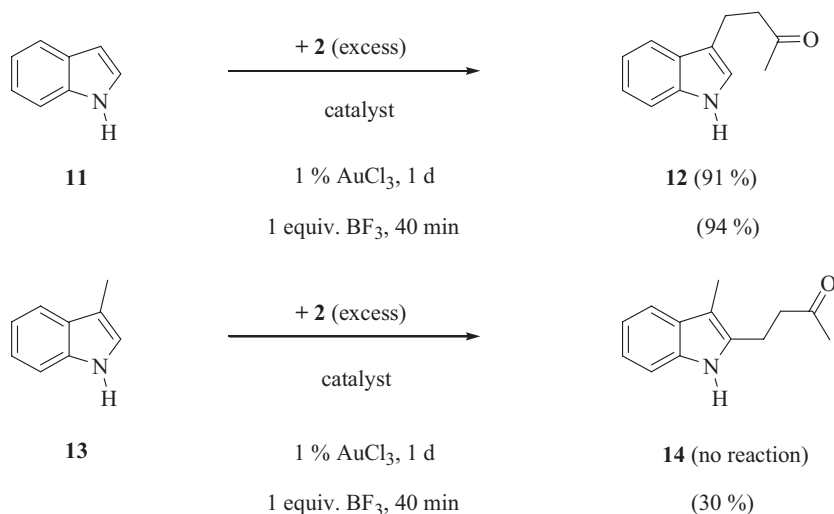
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Scheme 2. Reactivity and selectivity of AuCl₃, HCl, and HBF₄ as catalysts in Friedel–Crafts-type reactions.

para-toluenesulfonic acid – a less nucleophilic Bronstedt acid – gave a similar result to AuCl_3 .

The advantage of AuCl_3 becomes obvious in the reaction with the acid sensitive azulene (**4**) – with protic catalysts of higher acidity such as hydrochloric acid it is recommended to begin working up after about two minutes reaction time, because of competing and product-consuming oligomerization processes, whereas with AuCl_3 a rather constant 50–55 % yield of the bis-product **5** is obtained both after 2 min and after 3 days reaction time.

For the 1,3,5-substituted trimethoxybenzene **6**, AuCl_3 is highly selective for the mono-adduct **7**, whereas the more reactive HBF_4 is appropriate for obtaining the bis-adduct **8**, again with excellent yield. Surprisingly AuCl_3 fails in the reaction with the 1,2,3-substituted trimethoxybenzene **9**. Obviously, this substitution pattern already induces significant steric hindrance at the 4-position, thus HBF_4 is needed as catalyst to achieve an acceptable yield. For the alkylation of indole (**11**) in the 3-position just 1 % AuCl_3 is sufficient to achieve an excellent yield. BF_3 -etherate – one equivalent is used – even catalyzes the alkylation of 3-methylindole (**13**) at the 2-position, but is somewhat inferior to bismuth nitrate [2, 3], which is reported to give a 46 % yield in this reaction. It should be emphasized that Friedel–Crafts reaction of MVK is limited to especially activated arenes. The catalysts tested failed, for example, with mesitylene, pyrene, 2,7-dimethoxynaphthalene, and even 1,4-dimethoxybenzene.

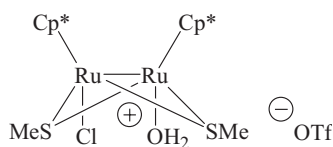


Scheme 3. Friedel–Crafts-type reactions with indoles.

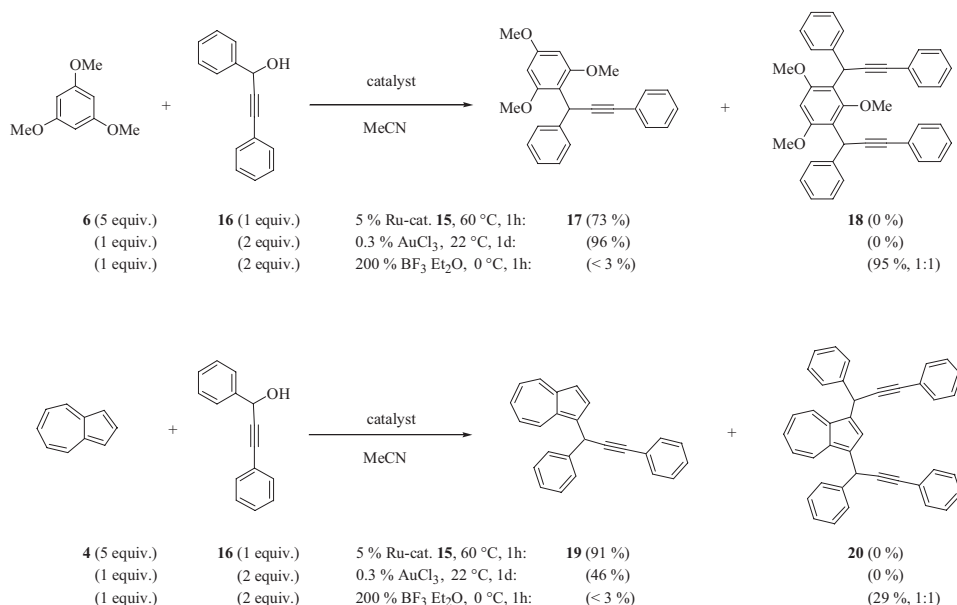
1.3.1.1.3 Alkylation of Arenes with Propargylic Alcohols

Because of its potential in synthesis, the propargylation of arenes is a focus of current interest. According to Yamamoto et al. the dinuclear cationic ruthenium complex **15** is exceptionally active in this type of reaction when applied at in 5 %

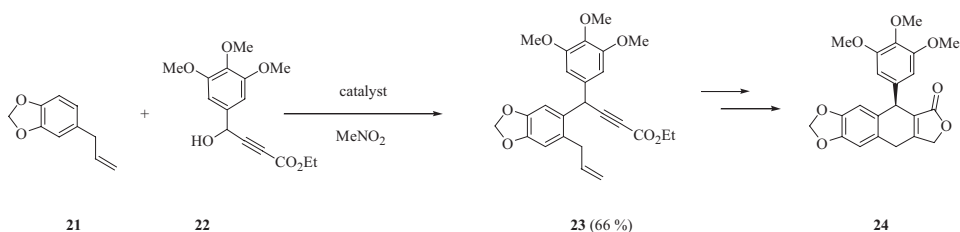
amounts at 60 °C [4]. For example, with propargylic alcohol **16** as the standard model reactant good to excellent yields of the mono-substitution products **17** and **19** are obtained from reaction with excess 1,3,5-trimethoxybenzene **6** and excess azulene **4**, respectively. Electrophilic (η -propargyl)ruthenium species are proposed as intermediates.

**15**

We have tested AuCl₃ and BF₃ etherate in comparison. Merely 0.3 % of the gold catalyst is sufficient to obtain 96 % isolated yield of the mono-substitution product **17** [5]. The reaction is performed at room temperature with two equivalents of propargylic alcohol **16**, thus demonstrating both outstanding reactivity and remarkable selectivity for the mono-substitution. Application of the classical Friedel–Crafts catalyst BF₃ etherate in stoichiometric amounts or in excess necessitates cooling, and results in rather clean formation of the sterically crowded bis-substitution product **18** as a mixture of the two diastereoisomers in the ratio 1:1.

**Scheme 4.** Propargylation of electron-rich arenes [4, 5].

Recently Toste et al. [6] introduced the air- and moisture-tolerant Re-complex (dppm)Re(O)Cl₃ as an alternative. Applied as catalyst in 5 % amounts (5 h at 65 °C) the propargylation of 1,2,3-trimethoxybenzene (**9**) with model reactant **15** is achieved with 92 % yield of the corresponding mono-substitution product. The potential of this method is highlighted by the successful synthesis of natural products such as β -apopicropodophyllin (**24**) (Scheme 5).



Scheme 5. Synthesis of β -apopicropodophyllin (**24**).

1.3.1.1.4 Conclusion

Classical Friedel–Crafts catalysts such as BF₃ etherate or Bronsted acids, which are applied in stoichiometric amounts or even in excess, still have their value, because they are relatively inexpensive yet powerful catalysts for C–H transformation at arenes and, most importantly, they are often successful when modern catalysts fail. Gold(III) chloride, at less than 1 %, has impressive reactivity under very moderate reaction conditions and its selectivity is exceptionally good. Friedel–Crafts type reactions with this catalyst are, however, restricted to very electron-rich arenes. Further studies should concentrate on increasing the electrophilicity of gold catalysts. New catalysts have emerged, for instance based on ruthenium and rhenium, which promise broad applicability based on alternative mechanisms. Catalysts based on rare earth metals are discussed in the next chapter.

Experimental

1,3-Bis-(3-oxobutyl)-azulene (**5**)

A mixture of 211 mg (3.00 mmol) MVK, 950 mg acetonitrile, and 300 mg (10 μ mol, 0.2 mol%) AuCl₃ was slowly added under argon to a vigorously stirred solution of 193 mg (1.50 mmol) azulene (**4**) in 2 mL acetonitrile. After 1 day at room temperature the reaction mixture was filtered through a small pad of silica (2 g) with an additional 5 mL acetonitrile as eluent. The solvent was removed in vacuo at 50 °C (from 15 mbar to 0.2 mbar) and the residue purified by flash chromatography on silica gel (petroleum ether *tert*-butyl methyl ether 2:1; *R*_F = 0.10). Recrystallization from CH₂Cl₂–diethyl ether yielded 201 mg (50 %) **15** as dark blue–green crystals (m.p. 63 °C). ¹H NMR (CDCl₃, 500 MHz): δ = 2.12 ppm (s, 6H), 2.87 (m, 4H), 3.31 (m, 4H), 7.00 (t, *J* = 9.9 Hz), 7.49 (t, *J* = 9.9 Hz), 7.60 (s, 1H), 8.17 (d, *J* = 9.9 Hz). ¹³C NMR (CDCl₃, 125 MHz): δ = 21.17 ppm (t), 30.11 (q), 45.16 (t), 121.12 (d), 127.12 (s), 133.07 (d), 135.92 (s), 136.47 (d), 137.73 (d), 208.42 (s).

1.3.1.2 Lanthanoid Triflates in Catalytic Amounts for Friedel–Crafts-type Reactions

Shu Kobayashi

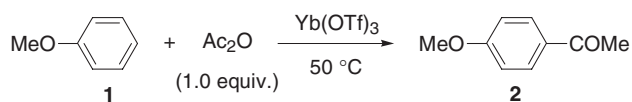
1.3.1.2.1 Introduction and Fundamental Examples

Friedel–Crafts acylation and alkylation are among the most fundamental and useful reactions for introducing functional substituents to aromatic rings [1], and are often used for industrial production of pharmaceuticals and agricultural chemicals, plastics, and liquid crystals, etc. These reactions were originally performed by using more than stoichiometric amounts of Lewis acids, for example aluminum trichloride (AlCl_3), because the Lewis acids are consumed by coordination with the aromatic ketones produced. As a result, a large amount of AlCl_3 and its waste after aqueous work-up procedures often causes serious environmental problems. To address this issue, several much effort was devoted to performing reactions using catalytic amounts of acidic promoters [2], or to recycling metal oxide catalysts, etc. [3]. Usually, however, substrates are limited and examples of truly efficient catalysts are few.

On the other hand, rare-earth trifluoromethanesulfonates (rare earth triflate, $\text{RE}(\text{OTf})_3$) have been found to work efficiently as Lewis acids even in aqueous media or in the presence of amines [4]. A catalytic amount of $\text{RE}(\text{OTf})_3$ enables several synthetically useful reactions, for example aldol, Michael, allylation, Mannich, Diels–Alder reactions, etc., to proceed. It has also been demonstrated that a small amount of $\text{RE}(\text{OTf})_3$ is enough to complete the reactions and that $\text{RE}(\text{OTf})_3$ can easily be recovered from the reaction mixture and can be reused. A key to accomplishing the catalytic processes was assumed to be the equilibrium between Lewis acids and Lewis bases, for example water, carbonyl compounds, and amines, etc. A similar equilibrium was expected between Lewis acids and aromatic ketones, and, thus, $\text{RE}(\text{OTf})_3$ -catalyzed Friedel–Crafts acylation was investigated [5].

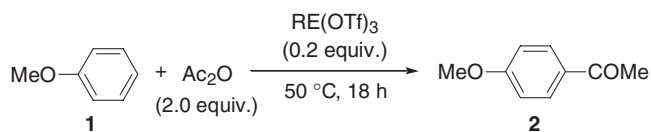
Reaction of anisole (**1**) with acetic anhydride was chosen as a model, and ytterbium trifluoromethanesulfonate (ytterbium triflate, $\text{Yb}(\text{OTf})_3$) was the first $\text{RE}(\text{OTf})_3$ representative used. Several reaction conditions were examined; the results are summarized in Table 1. When acetic anhydride, acetonitrile, or nitromethane was used as a solvent (entries 4–10), the reaction mixture became homogeneous and the acylation reaction proceeded smoothly. Nitromethane gave the highest yield of 4-methoxyacetophenone (**2**) (entries 7–10). On the other hand, in carbon disulfide, dichloroethane, or nitrobenzene (entries 1–3), the reaction mixture was heterogeneous and the yield of **2** was low. It was noted that the acylation proceeded quantitatively when a catalytic amount of $\text{Yb}(\text{OTf})_3$ was used (0.2 equiv., entry 9). Even when 0.05 equiv. of the catalyst was employed, **2** was obtained in 79 % yield (entry 10).

Other $\text{RE}(\text{OTf})_3$ were also examined as catalysts in the reaction of **1** with acetic anhydride (Table 2). Catalytic amounts of all the $\text{RE}(\text{OTf})_3$ listed effectively mediated the acylation of **1**. Among these, scandium trifluoromethanesulfonate (scandium triflate, $\text{Sc}(\text{OTf})_3$) [6] or $\text{Yb}(\text{OTf})_3$ was superior to other $\text{RE}(\text{OTf})_3$ and afforded the acylation product **2** quantitatively. When, on the other hand, lanthanum trifluoromethanesulfonate (lanthanum triflate, $\text{La}(\text{OTf})_3$) was used, the yield of **2** was relatively low. The yields shown in Table 2 may reflect the catalytic activity of respective $\text{RE}(\text{OTf})_3$.

Table 1. Yb(OTf)₃-catalyzed Friedel–Crafts acylation of **1**.

Entry	Yb(OTf) ₃ equiv.	Time h	Solvent	Yield %
1	1.0	24	CS ₂	ND ^{a)}
2	1.0	24	ClCH ₂ CH ₂ Cl	8
3	1.0	20	PhNO ₂	32
4	1.0	3	Ac ₂ O	53
5	0.2	18	Ac ₂ O	48
6	1.0	24	MeCN	52
7	1.0	20	MeNO ₂	78
8	0.2	48	MeNO ₂	60
9 ^{b)}	0.2	18	MeNO ₂	99
10 ^{b)}	0.05	48	MeNO ₂	79

a) Not detected. b) Two equiv. of Ac₂O were used.

Table 2. Effect of rare earth metal triflates (RE(OTf)₃).

RE	Yield/%	RE	Yield/%
Sc	99	Gd	77
Y	69	Dy	85
La	41	Ho	79
Pr	87	Er	78
Nd	79	Tm	84
Sm	80	Yb	99
Eu	78	Lu	81

The difference between the catalytic activity of $\text{Yb}(\text{OTf})_3$ and $\text{Sc}(\text{OTf})_3$ is shown in Table 3. When the acylation of **1** was performed in a shorter reaction time (4 h), $\text{Sc}(\text{OTf})_3$ gave a higher yield of **2** than $\text{Yb}(\text{OTf})_3$. In the acylation of mesitylene (**3**), $\text{Sc}(\text{OTf})_3$ also gave a much higher yield of aromatic ketone **4** in a shorter reaction time (73 %, 1 h) than $\text{Yb}(\text{OTf})_3$ (16 %, 18 h). These results show that $\text{Sc}(\text{OTf})_3$ is the most active Friedel–Crafts catalyst among $\text{RE}(\text{OTf})_3$. In the periodic table, scandium lies above yttrium and the lanthanides and its chemical behavior is known to be intermediate between aluminum and lanthanides [7]. Scandium oxide is more basic than aluminum oxide and more acidic than lanthanide oxides. In addition, its ionic radius is the smallest among rare earths, and thus it would be reasonable to conclude that $\text{Sc}(\text{OTf})_3$ is the strongest Lewis acid among the $\text{RE}(\text{OTf})_3$. The effect of using different amounts of $\text{Sc}(\text{OTf})_3$ in the acetylation of **1** is summarized in Table 4. The reaction proceeded smoothly in a few hours if a catalytic amount of $\text{Sc}(\text{OTf})_3$ was used, and 6200 % yield of acetylation product **2** (based on the catalyst) was obtained when 0.01 equiv. $\text{Sc}(\text{OTf})_3$ was employed (entry 3).

Table 3. Catalytic activity of $\text{Yb}(\text{OTf})_3$ and $\text{Sc}(\text{OTf})_3$.

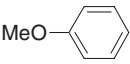
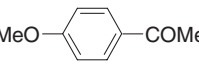
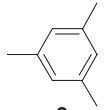
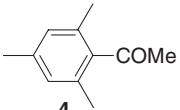
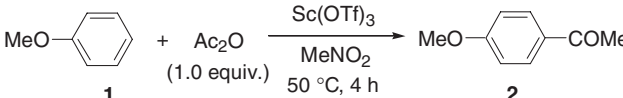
Ar-H + Ac ₂ O (2 equiv.)		Catalyst (0.2 equiv.)	Ar-COMe	
		MeNO ₂ , 50 °C		
Ar-H	Catalyst	Product	Time/h	Yield/%
 1	$\text{Yb}(\text{OTf})_3$	 2	4	55
	$\text{Sc}(\text{OTf})_3$		4	89
 3	$\text{Yb}(\text{OTf})_3$	 4	18	55
	$\text{Sc}(\text{OTf})_3$		1	89

Table 4. Effect of the amount of $\text{Sc}(\text{OTf})_3$.



COc1ccc(cc1) + Ac2O >> COc1ccc(cc1)C(=O)Me
1 (1.0 equiv.) $\xrightarrow[\text{MeNO}_2, 50\text{ }^\circ\text{C, 4 h}]{\text{Sc}(\text{OTf})_3}$ **2**

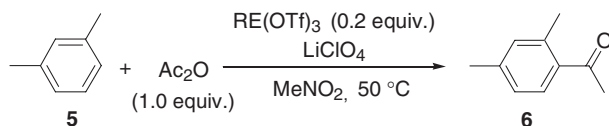
Entry	Sc(OTf) ₃ /equiv.	Yield/% ^{a)}
1	0.2	89 (445)
2	0.05	76 (1520)
3	0.01	62 (6200)

^{a)} The number in parentheses is the yield based on $\text{Sc}(\text{OTf})_3$.

In the $\text{RE}(\text{OTf})_3$ -catalyzed Friedel–Crafts acylation, the acylation of aromatic compounds with electron-donating substituents, for example anisole and mesitylene, proceeded smoothly whereas the reactivity of benzene, toluene, and xylenes was low under the same conditions. On the other hand, it was revealed that the catalyst activity of $\text{RE}(\text{OTf})_3$ was increased when combined with LiClO_4 , and that the acceleration effect was strongly dependent on the amount of LiClO_4 .

The reaction of *m*-xylene (**5**) with acetic anhydride was studied in the presence of $\text{Sc}(\text{OTf})_3$ or $\text{Yb}(\text{OTf})_3$ (a representative $\text{RE}(\text{OTf})_3$). The yields were increased, depending on the amount of LiClO_4 in both cases (Table 5). In the absence of LiClO_4 , $\text{Sc}(\text{OTf})_3$ catalyzed the acylation of **5** to afford the desired aromatic ketone (**6**) in only 12 % yield. When $\text{Sc}(\text{OTf})_3$ was combined with 10 equiv. LiClO_4 , however, the yield was improved to 89 %. With $\text{Yb}(\text{OTf})_3$ no product was obtained in the absence of LiClO_4 and 83 % yield of the desired product was obtained in the presence of 6 equiv. LiClO_4 .

Table 5. Acceleration of acylation by LiClO_4 .



RE = Sc ^{a)}		RE = Yb ^{b)}	
LiClO_4	Yield	LiClO_4	Yield
equiv.	%	equiv.	%
None	12	None	ND ^{c)}
0.4	12	0.4	8
0.8	28	0.8	17
1.0	36	1.0	22
2.0	51	2.0	38
4.0	61	4.0	67
6.0	82	6.0	83
8.0	88		
10.0	89		

a) 1 h. b) 4 h. c) Not detected.

1.3.1.2.2 Mechanism

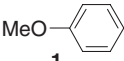
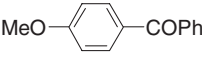
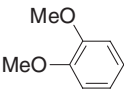
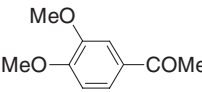
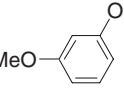
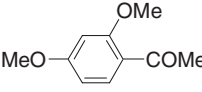

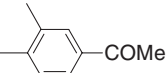

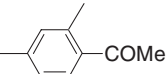
Although the precise mechanism of $\text{RE}(\text{OTf})_3$ -catalyzed Friedel–Crafts acylation has not been reported, a key step is believed to be ready release of $\text{RE}(\text{OTf})_3$ from $\text{RE}(\text{OTf})_3$ –aromatic ketone complexes. Whereas LiClO_4 worked well in combination with $\text{RE}(\text{OTf})_3$, other metal salts such as NaClO_4 , $\text{Mg}(\text{ClO}_4)_2$, LiOTf , and LiBF_4 , etc., were not effective. It was reported that ionic species such as $\text{CH}_3\text{CO}^+\text{SbF}_6^-$, $\text{CH}_3\text{CO}^+\text{PF}_6^-$, $\text{CH}_3\text{CO}^+\text{BF}_4^-$, and $\text{CH}_3\text{CO}^+\text{AsF}_6^-$, were active acylating agents in which the acylium cation was stabilized by the weakly basic counter anion [8]. It was also known that acetyl perchlorate, $\text{CH}_3\text{CO}^+\text{ClO}_4^-$, generated in situ by reaction of carboxylic acid or carboxylic anhydride with perchloric acid in aqueous media, had high reactivity in the acylation of aromatic compounds [9]. Furthermore, it was reported that lithium perchlorate (LiClO_4) formed a stable acylium cation when mixed with an acylating agent in the presence of an antimony or hafnium compound. [10] It was therefore expected that an acylium cationic species such as acyl perchlorate generated in the presence of $\text{RE}(\text{OTf})_3$ and LiClO_4 would react with aromatic compounds to afford the corresponding aromatic ketones.

As an trial to generate an active acylium cation species in the presence of $\text{RE}(\text{OTf})_3$, a combination of $\text{Sc}(\text{OTf})_3$ (0.2 equiv.) and an alkali or alkaline earth metal salt (2.0 equiv.) was investigated in the reaction of *m*-xylene (**5**) with acetic anhydride. Without the metal salt, acylation product **6** was obtained only in 12 % yield. When, however, the acylation was accelerated by adding LiClO_4 , the yield was improved to 50 %. Interestingly, sodium or magnesium perchlorate was not effective. In the absence of $\text{Sc}(\text{OTf})_3$, LiClO_4 was not soluble in the reaction mixture and no acylation product was obtained. When $\text{Sc}(\text{OTf})_3$ was added to a suspension of LiClO_4 , acetic anhydride, and *m*-xylene (**5**) in nitromethane, the heterogeneous mixture changed to a dark-red homogeneous solution and the acylation reaction began to proceed.

1.3.1.2.3 Scope and Limitation

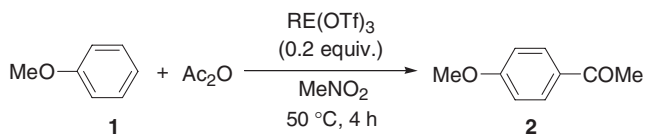
Several substituted benzenes were subjected to $\text{Yb}(\text{OTf})_3$ or $\text{Sc}(\text{OTf})_3$ -catalyzed Friedel–Crafts acylation using acetic anhydride, acetyl chloride, benzoic anhydride, or benzoyl chloride as acylating agent (Table 6). Acetylation of *o*- and *m*-dimethoxybenzene proceeded smoothly to afford the desired acetylated products in excellent yields. Although xylenes gave the acetylated adducts in lower yields, benzene and toluene reacted sluggishly. Acetyl chloride was effective in the reaction, and yields were 5–10 % lower than those obtained using acetic anhydride. Both benzoic anhydride and benzoyl chloride enabled successful benzoylation. Anisole (**1**) reacted with benzoic anhydride and benzoyl chloride smoothly in the presence of a catalytic amount of $\text{Sc}(\text{OTf})_3$ to give 4-methoxybenzophenone in high yields (entries 1 and 2). In each reaction formation of other isomers was not observed.

Table 6. RE(OTf)₃-catalyzed Friedel–Crafts acylation.

Ar-H + Acylating Agent		RE(OTf) ₃ (0.2 equiv.) MeNO ₂ , 50 °C		Ar-COMe		
Entry	Ar-H	RE(OTf) ₃	Acylating agent	Time/h	Product	Yield/%
1		Sc(OTf) ₃	PhCOCl	18		79
2		Sc(OTf) ₃	(PhCO) ₂ O	18		90
3		Sc(OTf) ₃	Ac ₂ O	1		99
4		Sc(OTf) ₃	Ac ₂ O	1		89
5		Yb(OTf) ₃	Ac ₂ O	18		22
6		Sc(OTf) ₃	Ac ₂ O	1		14
7		Yb(OTf) ₃	Ac ₂ O	18		25
8		Sc(OTf) ₃	Ac ₂ O	1		11

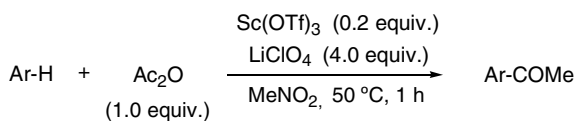
The reusability of the catalyst is one of the major advantages of using RE(OTf)₃ as a Friedel–Crafts catalyst. RE(OTf)₃ can be easily recovered from the reaction mixture by simple extraction. The catalyst is soluble in the aqueous layer rather than in organic layer, and is recovered by removing water to give a crystalline residue, which can be re-used without further purification. The efficiency of recovery and the catalytic activity of the reused RE(OTf)₃ were examined in the reaction of **1** with acetic anhydride using Yb(OTf)₃ and Sc(OTf)₃. As shown in Table 7, more than 90 % of Yb(OTf)₃ and Sc(OTf)₃ were easily recovered, and the yields of acylation product **2** in the second and the third uses were almost the same as in the first.

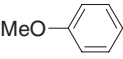
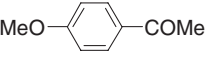
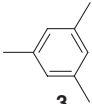
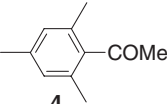

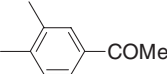
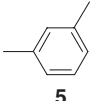
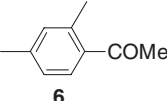

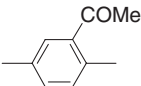

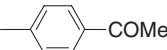
In the Sc(OTf)₃–LiClO₄-system, wider substrate scope was observed as is shown in Table 8. Each acylation reaction in the Table gave a single acylation product and formation of other isomers was not observed. Acetylation of anisole (**1**) resulted in excellent yield of the product (entry 1). Mesitylene (**3**) and xylenes were transformed to 2,4,6-trimethylacetophenone and dimethylacetophenones, respectively, in moderate yields (entries 2–5). It is noteworthy that toluene was acylated by the Sc(OTf)₃–LiClO₄ system to give 4-methylacetophenone in 48 % yield (entry 6) but the acylation did not proceed in the absence of LiClO₄. Furthermore, recovery and reuse of the RE(OTf)₃–LiClO₄ system were performed successfully. As shown in Table 9, the yields of **6** in the second and third uses of the catalyst system were almost the same as that in the first use.

Table 7. Reuse of RE(OTf)₃ in the acetylation of **1**.

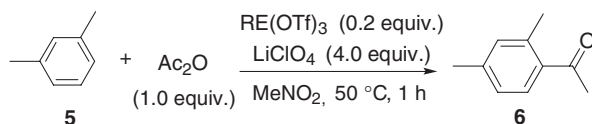
RE(OTf) ₃	No. of times used	Yield/%	Recovery of RE(OTf) ₃ /%
Sc(OTf) ₃ ^{a)}	1	89	94
	2	93	90
	3	91	92
Yb(OTf) ₃ ^{b)}	1	70	93
	2	69	90
	3	71	92

^{a)} One equiv. of Ac₂O was used. ^{b)} Two equiv. of Ac₂O were used.

Table 8. Sc(OTf)₃-catalyzed acylation in LiClO₄–MeNO₂.

Entry	Ar-H	Product	Yield/%
1			96
2			93
3			55
4			61
5			16
6 ^{a)}			47

^{a)} 20 h.

Table 9. Catalytic activity of recovered $\text{RE}(\text{OTf})_3\text{--LiClO}_4$.

RE	Number of times used	Yield/%	Recover of catalyst/%
Sc	1	61	96
	2	55	94
	3	53	87
Yb ^{a)}	1	68	95
	2	73	99
	3	70	91

^{a)} LiClO_4 (10.0 equiv.) was used and the reaction time was 4 h.

For catalytic Friedel–Crafts acylation, several excellent catalysts other than RE have recently been reported [11]. Although some are more active than RE, most are water-sensitive and cannot be recovered and reused after the reactions.

Experimental

Typical Procedure for $\text{RE}(\text{OTf})_3$ -catalyzed Friedel–Crafts Acylation

A mixture of $\text{Yb}(\text{OTf})_3$ (620 mg, 1 mmol), anisole (1, 540 μL , 5 mmol), and acetic anhydride (940 μL , 10 mmol) in nitromethane (5 mL) was stirred at 50 °C for 4 h. After dilution with water (10 mL), the mixture was extracted with dichloromethane. The organic layers were combined and dried over NaSO_4 . After filtration and evaporation of the solvents, the crude mixture was purified by column chromatography on silica gel to afford 4-methoxyacetophenone (**2**). The aqueous layer was concentrated in vacuo to give a crystalline residue, which was heated at 190 °C for 4 h in vacuo to afford 576.6 mg (93 %) $\text{Yb}(\text{OTf})_3$ as colorless crystals. The recovered $\text{Yb}(\text{OTf})_3$ was reused in the next acylation reaction. All products of the acylation of aromatic compounds shown in this chapter are known compounds and are commercially available.

Typical Procedure for $\text{RE}(\text{OTf})_3\text{--LiClO}_4$ System-catalyzed Friedel–Crafts Acylation

Acetic anhydride (470 μL , 5 mmol) was added to a suspension of $\text{Sc}(\text{OTf})_3$ (490 mg, 1 mmol), *m*-xylene (610 μL , 5 mmol), and LiClO_4 (2130 mg, 20 mmol) in nitromethane (5 mL) and the suspension changed to a dark-red homogeneous solution. After stirring at 50 °C for 1 h, the reaction mixture was diluted with water (10 mL), and the aqueous layer was extracted with dichloromethane (3×10 mL). The organic layers were combined and dried over NaSO_4 . After filtration and evaporation of the solvents, the crude mixture was purified by column chromatography on silica gel to afford 2,4-dimethylacetophenone (**6**). The aqueous layer was

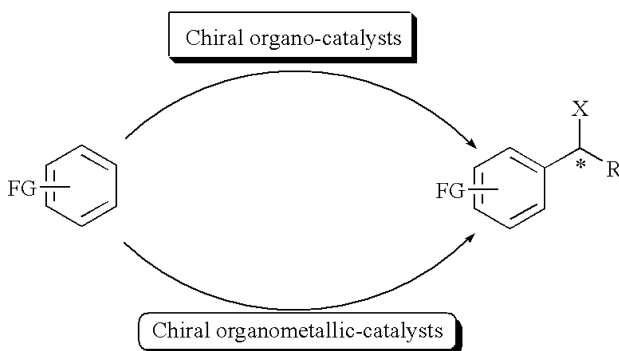
concentrated to give crystalline residues which were heated at 190 °C for 4 h in vacuo to afford a mixture of LiClO_4 and $\text{Sc}(\text{OTf})_3$ (2510 mg, 96 %). The recovered catalyst was reused in the next acylation reaction.

1.3.1.3 Enantioselective Friedel–Crafts Type Alkylation Reactions

Marco Bandini, Alfonso Melloni, and Fabio Piccinelli

1.3.1.3.1 Introduction and Fundamental Examples

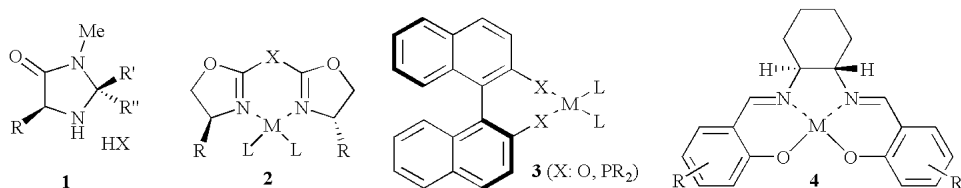
Although Friedel–Crafts (F–C) alkylation reactions are among the longest known organic transformations requiring Lewis acids (LA) as promoters[1], only in recent decades significant improvements in the design and development of new catalytic stereoselective procedures have been reported [2]. In this scenario, two different, and to some extent complementary, approaches have been recognized as being highly effective in enantioselective electrophilic alkylations of electron-rich aromatic compounds: (1) the use of small chiral organic molecules mimicking the catalytic activity of enzymes, and (2) the employment of chiral organometallic complexes, made by use of enantiomerically pure organic ligands (*chiraphor unit*) with metal salts (*catalaphor unit*), acting as chiral Lewis acids (Scheme 1).



Scheme 1. Organic and organometallic chiral catalysts: different approaches for stereocontrolled alkylation of arenes.

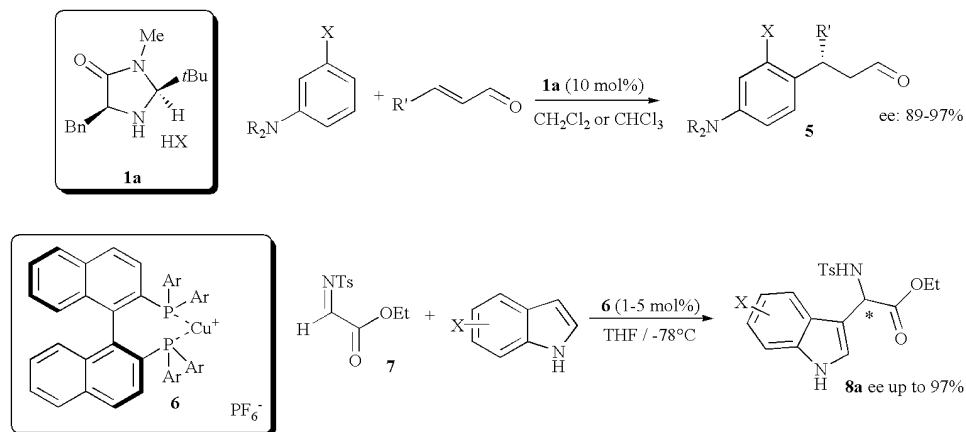
Both strategies involve the key interaction between the chiral catalyst and the electrophilic reagent (usually a carbonyl compound) but their complementary behavior lies in the nature of organic molecules that can be coupled with the aromatic ring. As a matter of fact, although organic catalysts such as chiral imidazolidinone salts (**1**) have proven successful in the enantioselective alkylation of arenes with aromatic and aliphatic α,β -unsaturated aldehydes (1,4-addition), enantiomerically pure organometallic catalysts (e.g. bisoxazoline, binaphthyl based ligand, and Schiff base–metal complexes **2–4**, Scheme 2) afforded remarkable results in the presence of ketones and carboxylic substrates (1,4-addition) and carbonyl moieties $\text{C}=\text{X}$ (1,2-addition). It is important to note that whereas organome-

tallic catalysts usually require strictly anhydrous reaction conditions to guarantee high levels of chemoselectivity and stereoselectivity, organic catalyst-based approaches are usually performed in aqueous media (*i*PrOH, H₂O) or in reagent-grade solvents (CH₂Cl₂, THF), to properly dissolve the imidazolidinone salt and achieve satisfying catalytic turnover numbers (TON) and turnover frequencies (TOF).



Scheme 2. Chiral catalysts for enantioselective F–C alkylations of aromatic compounds.

Two examples of such applications are outlined in Scheme 3. In the first one imidazolidinone **1a** 10 mol% catalyzed the conjugated addition of a plethora of variously substituted *N,N*-disubstituted anilines to α,β -unsaturated aldehydes to afford highly enantiomerically enriched β -aryl aldehydes **5** (ee: 89–97%) in good yields (>73%) [3]. On the other hand, the use of cationic BINAP-Cu complexes **6** (1–5 mol%) was found to be effective in the stereocontrolled 1,2-addition of indoles to the *N*-tosyl- α -imino ester **7** in THF at -78 °C [4].

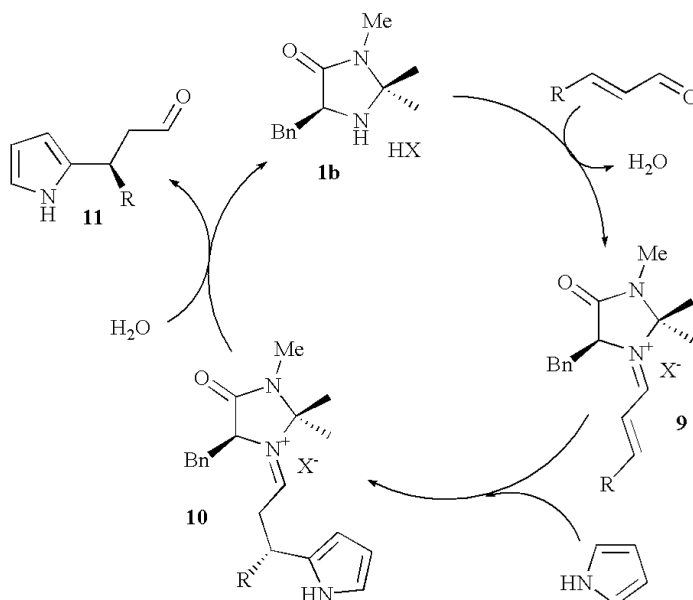


Scheme 3. Strategies for LUMO-lowering activation of electrophiles in stereoselective F–C alkylation.

1.3.1.3.2 Mechanism

Detailed mechanistic studies have been carried out for both the strategies of activation of electrophiles (E). In particular, the former stoichiometric Lewis acid mediated F–C version has been mechanistically well established and the formation of transient [LA–E] species is well known to be involved in the course of the reaction [5]. More recently, the combined use of Lewis acids (In^{III}, Ga^{III}, Bi^{III}, RE^{III}),

guaranteeing kinetically labile formation of the catalyst–product adduct, with effective scavengers enabled widespread substitution of the pioneering stoichiometric technologies with cleaner catalytic alternatives. Analogously, in organo-catalyst-mediated F–C alkylations the intermediate formation of the highly reactive chiral iminium ion **9** enables remarkable LUMO-lowering activation of the α,β -unsaturated aldehyde with consequent regioselective conjugate addition of the aromatic system (i.e. pyrrole) [6]. The final hydrolysis of the chiral quaternary ammonium salt **10** yields the desired β -pyrrolyl aldehyde and releases the chiral auxiliary for the ongoing process. A pictorial representation of the proposed catalytic cycle is depicted in Scheme 4. In this context, the mineral acid used as co-catalyst (20 mol%) revealed to be very important in the stereochemical outcome of the process and in the alkylation of pyrroles TFA provides the optimum reaction conditions. Finally, on the basis of theoretical computations the authors suggest a hypothetical incoming trajectory of the aromatic rationalizing the role of the chiral catalyst in determining the absolute configuration of the product.



Scheme 4. Proposed mechanistic pathway for the stereoselective organo-catalyzed F–C alkylation of pyrroles.


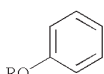
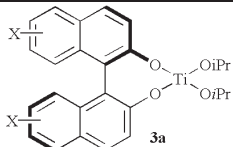
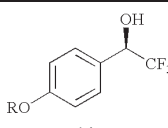
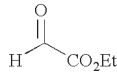
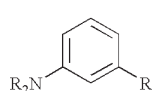
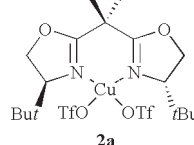
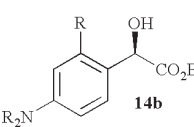
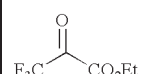
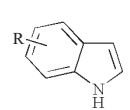
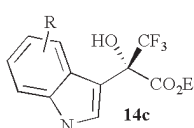
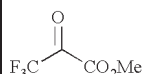
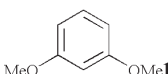
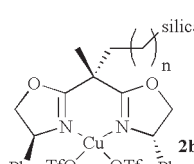
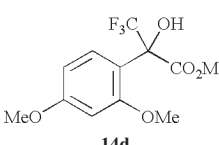
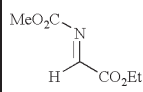
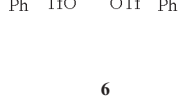
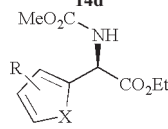
1.3.1.3.3 Scope and Limitations

Until now, three main F–C transformations have been used for catalytic stereoselective formation of benzylic carbon stereocenters – 1,2-addition of arenes to carbonyl ($C=X$, X : O, NR) moieties, 1,4-addition of arenes to electron-deficient C–C double bonds, and ring-opening reaction of epoxides.

In the first strategy chiral organometallic complexes are used to differentiate the enantiotopic faces of the carbonyl moiety, providing a powerful route to the

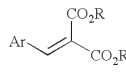
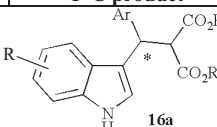
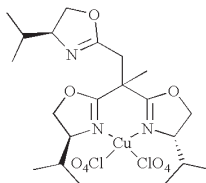
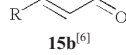

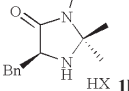
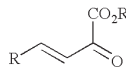
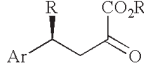
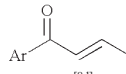
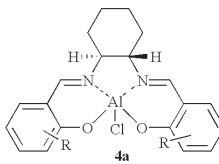
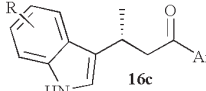
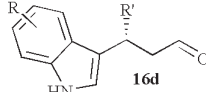
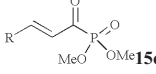
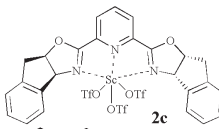
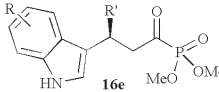
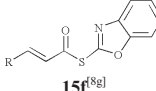
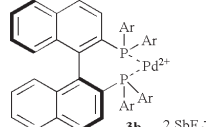
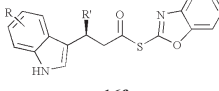
preparation of enantiomerically enriched α -aryl/heteroaryl esters. The presence of a two-site binding (chelating) interaction between the Lewis acid metal center and the electrophilic substrate is generally required to achieve high stereoselectivity. Therefore, 1,2- and 1,3-dicarbonyls have been found to be suitable candidates for such transformations. A brief summary of the most recent, straightforward enantioselective 1,2-type alkylation procedures is presented in Table 1. Highly enantiomerically pure α -hydroxy esters bearing tertiary and quaternary benzylic stereocenters (**14b–d**) are synthesized in good yields by using chiral Cu(I) and Ti(IV)-based Lewis acids. Moreover, synthetic useful optically active aromatic and hetero-aromatic α -amino esters **8a–b** are isolated in excellent yields by alkylation of electron-rich aromatic C–H bonds with α -imino esters (**7**, **12e**).

Table 1. Asymmetric catalyzed aromatic C–H addition of aromatics to C=X.

<div style="display: flex; align-items: center; justify-content: center;"> <div style="border: 1px solid black; padding: 2px 5px; margin: 0 5px;">Carbonyl</div> <div style="margin: 0 5px;">+</div> <div style="border: 1px solid black; padding: 2px 5px; margin: 0 5px;">Arene</div> </div>		Catalyst	<div style="display: flex; align-items: center; justify-content: center;"> <div style="border: 1px solid black; padding: 2px 5px; margin: 0 5px;">F-C product</div> </div>	
 12a ^[7a]	 13a	 3a	 14a	Y: 66-97% ee: 68-90%
 12b ^[7b]	 13b	 2a	 14b	Y: 19-84% ee: 77-95%
12b ^[7c]	13b	3a	14b	Y: 85-99% ee: 80-97%
 12c ^[7d]	 13c	2a	 14c	Y: 61-94% ee: 83-94%
 12d ^[7e]	 3d	 2b	 14d	Y: 72% ee: 92%
 12e ^[7f]	13b,c/furanes	 6	 8b	Y: 24-82% ee: 59-96%

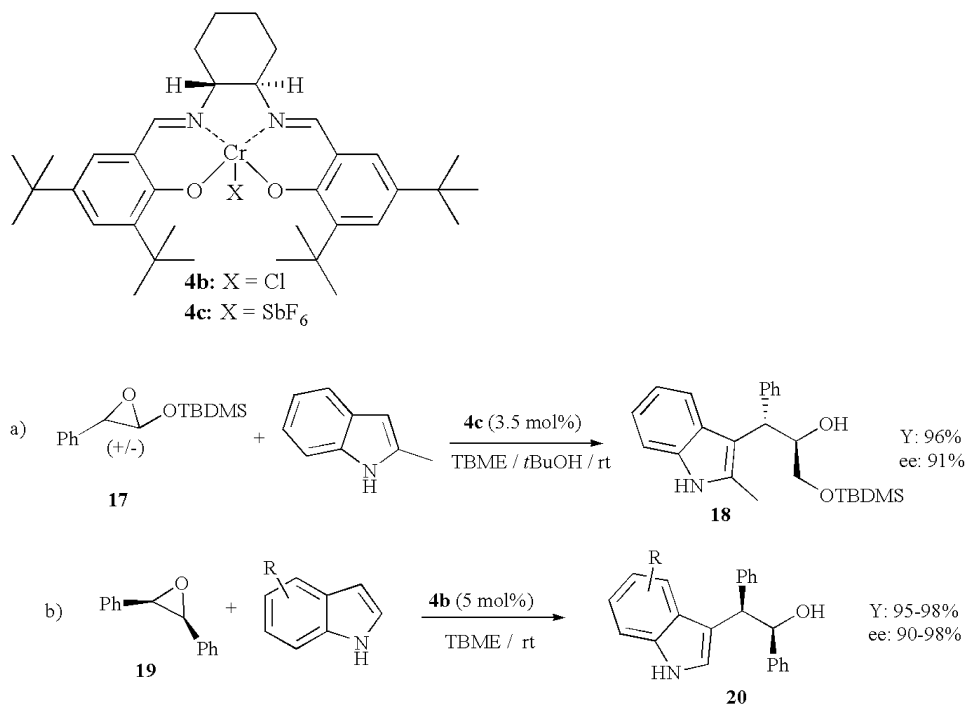
The second approach is particularly suitable for the synthesis of carbonyl and carboxylic compounds bearing β -aryl/heteroaryl benzylic stereocenters. Both organic [9] and organometallic chiral catalysts provide high levels of chemical and optical yield in these C–H transformations (Table 2). The high regioselectivity normally

Table 2. Asymmetric F–C alkylations by conjugated C–H addition to electron-poor C–C double bonds.

<div>Carbonyl</div> + <div>Arene</div>		<div>Catalyst</div>	<div>F-C product</div>	
Carbonyl	Arene	Catalyst	F-C product	Yield/ee
 15a ^[8a]	13c	2a	 16a	Y: 50-99% ee: 46-69%
15a ^[8b]	13c	 2b	16a	Y: 73-99% ee: 60-92%
 15b ^[6]	 13e	 1b	11	Y: 68-90% ee: 87-99%
 15c ^[8c]	6/furanes/13d	2a	 16b	Y: 65-99% ee: 60-99%
 15d ^[8d]	13c	 4a	 16c	Y: 70-98% ee: 49-89%
15b ^[8e]	13c	1a	 16d	Y: 80-98% ee: 89-97%
 15e ^[8f]	13c	 2c	 16e	Y: 51-88% ee: 80-99%
 15f ^[8g]	13c	 3b 2 SbF ₆ [–]	 16f	Y: 20-80% ee: 56-86%

encountered in these 1,4-additions (enones and α,β -unsaturated carboxylic compounds) is ascribed to the preferential attack of the arenes (soft nucleophiles) on the softer electrophilic β -position of the conjugate system. On the other hand, it should be stressed that the attempt to carry out a Lewis acid mediated Michael-type F–C alkylation with α,β -unsaturated aldehydes usually affords a complex mixture of compounds which results from competitive oligomerization of the electron-rich arene with the desired conjugate C–H addition. Then, use of a suitable metal-free chiral organic activator prevents this possibility providing the β -aryl aldehydes with high enantiomeric excesses.

The third route to catalytic stereoselective activation of C–H (sp^2) bonds has been investigated only recently by our group. It involves stereoselective kinetic resolution of racemic aromatic epoxides by indoles in the presence of catalytic amounts of [SalenCrSbF₆] complex (**4c**) [10]. Peculiarly, kinetic resolution processes enable the synthesis of both unconverted epoxides and the F–C adduct in high ee simply by a careful tuning of the initial ratio of reagents. In particular, by using excess epoxide, the ring-opening product is isolated in high yield and excellent enantioselectivity (up to 91 %, Scheme 5a). *meso*-stilbene oxide can, moreover, also be effectively desymmetrized (ee: 90–98 %) by use of a range of substituted indoles in the presence of commercially available chiral [SalenCrCl] **4b** (Scheme 5b).



Scheme 5. Enantioselective kinetic resolution of 1,2-disubstituted epoxides (a) and desymmetrization of *meso* stilbene-oxide (b) with indoles catalyzed by **4b–4c**.

Experimental

(*R*)-3-(1-Methyl-1*H*-indol-3-yl)-butanal (16d)

A solution of (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (**1a**, 24.6 mg, 0.10 mmol) in CH₂Cl₂ (0.85 mL) and isopropanol (0.15 mL), was treated with TFA (7.7 μ L, 0.10 mmol) and stirred for 5 min before addition of crotonaldehyde (125 μ L, 1.50 mmol). After stirring for an additional 10 min the 1-methyl-1*H*-indole (**13c**, 64 μ L, 0.50 mmol) was added in one portion. The resulting suspension was stirred at constant temperature (-83 °C) until complete consumption of the indole was observed by TLC (19 h). The reaction mixture was then passed cold through a silica gel plug with Et₂O and then concentrated. The resulting residue was purified by silica gel chromatography (benzene) to afford the title compound as a colorless oil (82 % yield, 92 % ee).

IR (film): 3054, 2960, 2824, 2722, 1720, 1616, 1550, 1474, 1374, 1329, 1241, 740 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) 9.75 (dd, *J* = 2.1, 2.1 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.32–7.21 (m, 2H), 7.12 (ddd, *J* = 1.5, 7.4, 8.1 Hz, 1H), 6.84 (s, 1H), 3.75 (s, 3H), 3.68 (dt, *J* = 6.9, 13.8 Hz, 1H), 2.88 (ddd, *J* = 2.7, 6.9, 16.2 Hz, 1H); 2.71 (ddd, *J* = 2.7, 6.9, 16.2 Hz, 1H); 1.44 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) 202.8, 137.2, 126.6, 125.2, 121.8, 119.1, 118.9, 118.8, 109.5, 51.2, 32.8, 26.0, 21.9; HRMS (CI) exact mass calcd. for (C₁₃H₁₅NO) requires *m/z* 201.1154, found *m/z* 201.1152. [α]_D = -4.2 (c 1.0, CHCl₃). The enantioselectivity was determined by subjecting approximately 10 mg of the title compound to excess NaBH₄ and 1 mL ethanol. After 15 min, the solution was treated with saturated aqueous NaHCO₃, and the mixture was extracted with CH₂Cl₂. The organic layer was separated, filtered through a silica gel plug and subjected to chiral HPLC analysis. Chiracel AD column (EtOH–*n*-hexanes 2:98, 1 mL min⁻¹); *S* isomer *t*_R = 25.2 min, *R* isomer *t*_R = 27.8 min.

(*S,R*-2-(2-Methyl-3-indolyl)-1-dimethyl-*t*-butylsilyloxy-2-phenylethanol (18)

A flamed, two-necked flask equipped with a magnetic stirring bar was charged with [SalenCrCl] **4b** (0.01 mmol) and activated molecular sieves 4 Å (100 mg). TBME (0.2 mL) was then added and the resulting solution was stirred under nitrogen at room temperature for 5 min. The solution was cooled to 0 °C and then **17** (0.3 mmol) and 2-methylindole (0.1 mmol) were added to the reaction mixture. Finally *t*-BuOH (0.1 mmol) was added and the reaction mixture stirred at 0 °C until GC analysis indicated complete conversion of 2-methylindole. The crude reaction mixture was diluted with Et₂O and filtered through celite. After evaporation of the solvent under reduced pressure the resulting residue was purified by silica gel chromatography (cyclohexane–Et₂O, 7:3) to afford the title compound as a white solid (96 % yield, 91 % ee).

Mp 109–111 °C. ¹H NMR (200 MHz, CDCl₃) -0.08 (s, 3H); 0.03 (s, 3H); 0.91 (s, 9H); 2.45 (s, 3H); 2.77 (d, *J* = 4.5 Hz, 1H); 3.45 (dd, *J* = 6.3, 10.2 Hz, 1H); 3.65 (dd, *J* = 3.6, 10.2 Hz, 1H); 4.32 (d, *J* = 10.2 Hz, 1H); 4.78–4.84 (m, 1H); 7.06–7.18 (m, 5H); 7.26–7.32 (m, 2H); 7.53 (dd, *J* = 0.9, 9.0 Hz, 1H); 7.63 (d, *J* = 7.8, 1H); 7.80 (br, 1H). ¹³C NMR (50 MHz, CDCl₃) -5.35 (2), 12.42, 18.25, 25.90 (3), 45.91, 65.62, 72.18, 110.24, 111.92, 119.32 (2), 120.82, 125.89, 127.45, 128.08 (2), 128.44 (2),

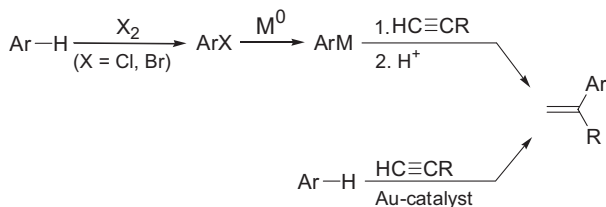
131.37, 135.23, 142.59. GC-MS m/z (relative intensity) 59 (8), 75 (20), 115 (10), 130 (15), 177 (15), 207 (25), 220 (100), 247 (15), 395 (10). Elem. Anal. Calcd. for $C_{24}H_{33}NO_2Si$: C, 72.86%; H, 8.41%; N, 3.54%. Found: C, 72.96%; H, 8.30%; N, 3.49%. Enantiomeric excess was evaluated by HPLC analysis: Chiracel OF, isocratic (*n*-hexane-*i*-PrOH, 88:12), flow 0.5 mL min⁻¹; *R,S* isomer t_R = 10.7 min; *S,R* isomer t_R = 15.7 min. $[\alpha]_D^{25}$ = +34.6 (*c* 0.53, CHCl₃).

1.3.1.4 Gold-catalyzed Hydroarylation of Alkynes

Manfred T. Reetz and Knut Sommer

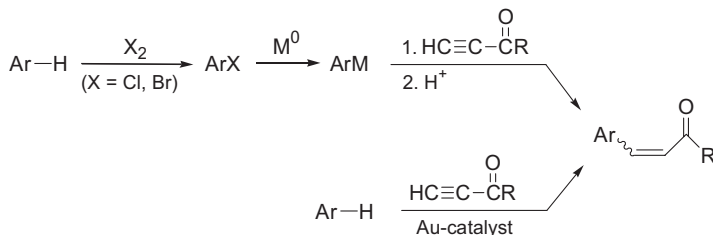
1.3.1.4.1 Introduction and Fundamental Examples

The conventional way of forming a C–C bond between an aromatic moiety and an alkyne with the formation of hydroarylation products involves the use of an aryl-metal reagent in a Cu- or Zr-catalyzed process or Ar_2CuLi in a stoichiometric reaction, followed by protonation of the vinylmetal intermediate [1]. Although these and other carbometalation reactions are reliable, the overall process requires several steps beginning with halogenation of an arene followed by transformation into the arylmetal reagent (Scheme 1). Atom and step economy would be greatly improved if a direct reaction between the arene and the alkyne could be developed (Scheme 1). Formally, this would involve C–H-activation of the arene.



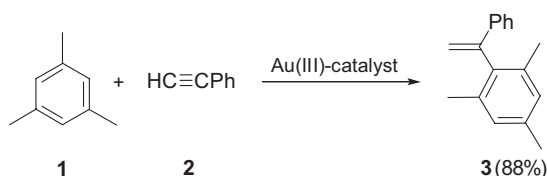
Scheme 1. Conventional (top) and direct (bottom) hydroarylation of alkynes.

If the R-group in the alkyne is a strongly electron-withdrawing moiety such as a carbonyl function, regioselectivity may be reversed, leading to the problem of *E/Z*-selectivity (Scheme 2). Irrespective of the type of alkyne, the one-step atom-economical process would need to be catalyzed because a simple thermal process does not provide the products.



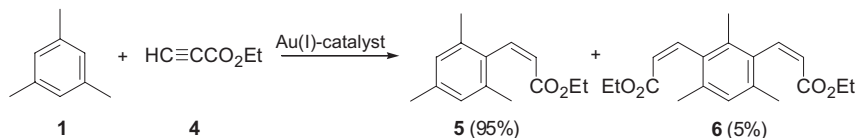
Scheme 2. Conventional (top) and direct (bottom) hydroarylation of electron-poor alkynes.

Recent work has shown that appropriate gold-catalysts are particularly suitable for direct hydroarylation of both kinds of alkyne [2], adding to previous catalytic systems based on other metals [3]. Depending upon the type of alkyne used, different gold catalysts must be employed. A typical reaction involving alkynes of the type noted in Scheme 1 is the hydroarylation of phenylacetylene **2** by mesitylene **1** (excess) with formation of olefin **3**. Whereas AuCl_3 affords only 20 % of the desired product **3** with rather long reaction times (60 °C/16 h), “cationization” with concomitant activation of AuCl_3 (5 mol%) by AgSbF_6 affords an excellent catalyst which mediates the smooth transformation within one hour (Scheme 3). The reaction can be optimized so that only 1.5 mol% of $\text{AuCl}_3/2\text{AgSbF}_6$ needs to be used (50 °C/4 h; 86 % **3**). This type of Au-catalyst is active for a fairly wide range of substrates, if the arene is electron-rich [2].



Scheme 3. Typical Au(III)-catalyzed hydroarylation of alkyne; 5 mol% $[\text{AuCl}_3/3\text{AgSbF}_6]$, 60 °C, 1 h, 3 equiv. **1**, yield determined by GC using the internal standard method.

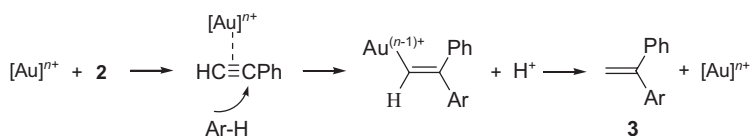
For electron-poor alkynes (Scheme 2) such as acetylene carboxylic acid ethyl ester **4**, the activated Au(III) catalysts lead to about 60 % of the product **5** as a 3.6:1 *Z/E* mixture. In contrast, Au(I) complexes of phosphines activated by AgSbF_6 or Lewis acids are much better suited, delivering nearly quantitative yields of **5** with complete *Z*-selectivity (Scheme 4) [2]. Only traces of the doubly vinylated compound **6** are observed as a side product. A particularly effective Lewis acid is $\text{BF}_3 \cdot \text{OEt}_2$, which also makes the catalytic system cheaper than those using AgSbF_6 as the activating agent.



Scheme 4. Typical Au(I)-catalyzed hydroarylation of electron-poor alkyne; 1 mol% $[\text{Ph}_3\text{PAuCl}/5\text{BF}_3 \cdot \text{OEt}_2]$, 50 °C, 14 h, 30 equiv. **1**, yields determined by GC using the internal standard method.

1.3.1.4.2 Mechanism

So far a detailed mechanistic study has not been completed, although initial observations are strongly suggestive [2, 4]. The synthetic results must be viewed within the context of other gold-catalyzed nucleophilic addition reactions of alkynes [5]. Cationization of AuCl_3 or AuCl complexes by AgSbF_6 or Lewis acids is required, but electrophilic auration of the arene as part of the hydroarylation seems unlikely in view of the known stoichiometric reaction of arylgold compounds with alkynes, which yields diarylacetylenes and not olefins [6d]. Thus, activation of the alkyne by $\text{Au}-\pi$ -complexation is likely to be involved, as has been postulated for other Au -catalyzed nucleophilic addition reactions [5]. For phenylacetylene **2**, the π -complex undergoes a type of electrophilic aromatic substitution with the electron-rich arene to form an intermediate vinyl- Au species [2, 4]. The concomitantly released H^+ protonates this intermediate, setting free the product **3** and regenerating the catalyst (Scheme 5). Regioselectivity is determined by electronic factors. Scheme 5 may be a simplification, because complete cationization with formation of true ion pairs may not occur at all steps. Strongly polarized neutral species could also be involved [7].



Scheme 5. Proposed mechanism for the hydroarylation of phenylacetylene **2**.

The mechanism of the Au(III) catalysis proposed in Scheme 5 implies the stereoselective formation of the new C–C bond which, of course, cannot be observed in the final product when terminal alkynes are used (the aryl group and the former alkyne hydrogen are situated at the same side of the double bond in the vinyl- Au intermediate). For the reaction of 1-phenyl-1-propyne and mesitylene **1** (see below, Table 1) the proposed mechanism should lead to preferential formation of the *Z* isomer which is, in fact, observed [2]. The formation of a small amount of *E* isomers can be explained by isomerization of the initially formed *Z* compound. Such isomerization was, in fact, observed directly in the case of related electron-poor alkynes [4].

In the Au(I) catalysis of electron-poor alkynes such as **4**, the catalytically active species is likely to be a cationic ligand-stabilized gold(I) π -complex, as in previously reported additions of oxygen nucleophiles to alkynes [5]. Gold catalysts are very soft and thus *carbophilic* rather than *oxophilic*. On the basis of this assumption a plausible mechanism can be formulated as shown in Scheme 6. The cationic or strongly polarized neutral Au(I) -catalyst coordinates to the alkyne, and nucleophilic attack of the electron-rich arene from the opposite side leads to the formation of a vinyl-gold intermediate **7** which is stereospecifically protonated with final formation of the *Z*-olefin **8** [2, 4]. Regioselectivity is dominated by elec-

tronic factors in a type of gold-catalyzed Michael addition. Preliminary NMR experiments are in line with this mechanism [2, 4].

Table 1. Hydroarylation of internal aryl-substituted alkynes with mesitylene **1**.^a

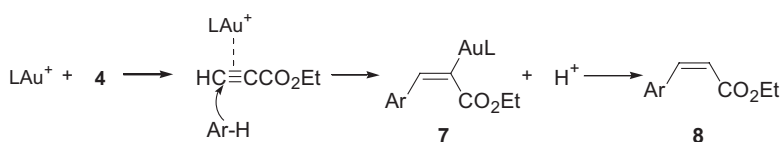
Entry	Alkyne	Time (h)	Product	Yield (%) ^b (Z:E)
1	PH-C≡C-CH ₃	16		(81) (70:30) ^d
2 ^c	PH-C≡C-CH ₃	4		79 (79:21) ^d
3 ^c	PH-C≡C-CH ₃	8		(94) (76:24) ^d
4	PH-C≡C-Ph	4		(5) (one isomer, double bond structure not determined)

^a Conditions (unless otherwise stated): 1.5 mol% AuCl₃, 3.0 mol% AgSbF₆, 50 °C, CH₃NO₂, 10 equiv. mesitylene **1**

^b Isolated yield. Values in parentheses refer to GC yields, determined with *n*-hexadecane as an internal standard

^c 4.5 mol% AgSbF₆ employed

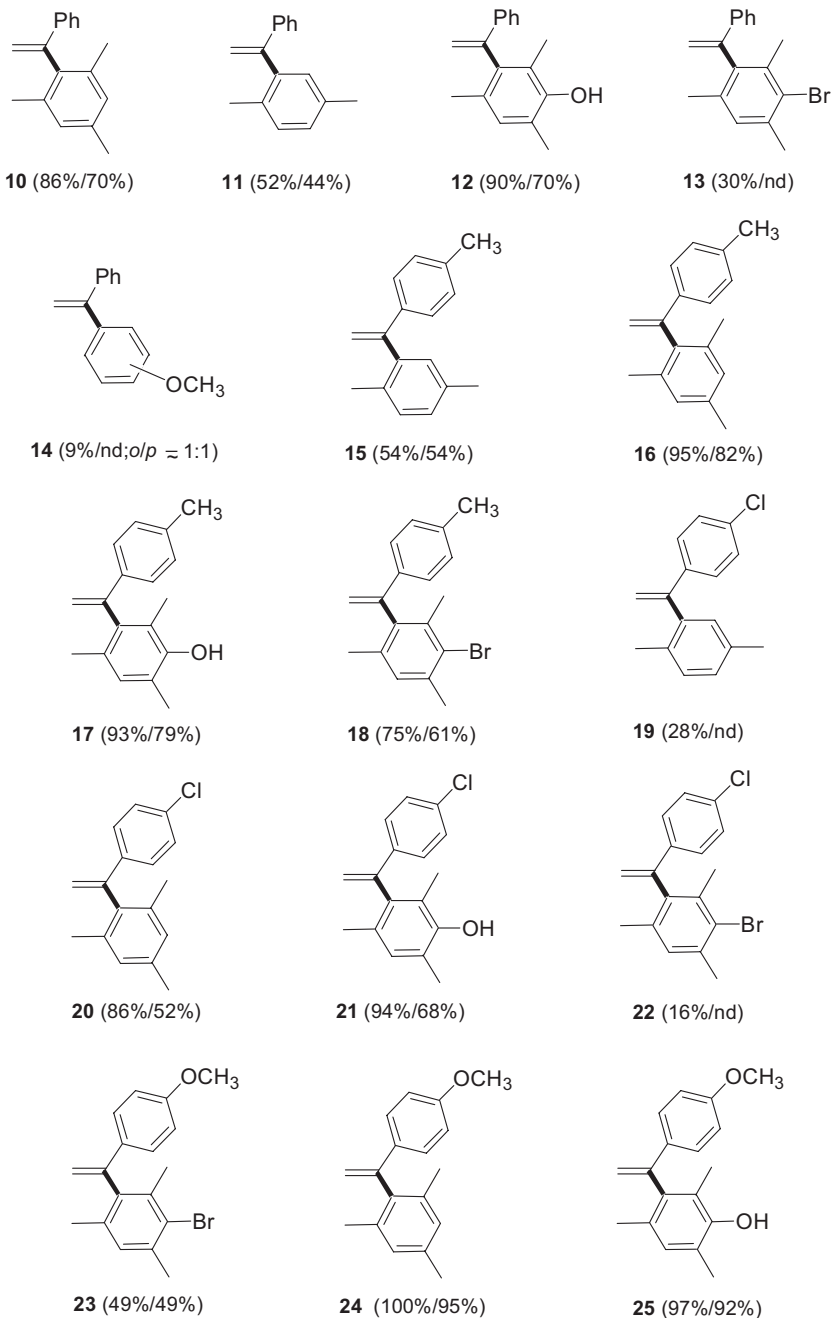
^d Determined by GC and/or NMR spectroscopy.



Scheme 6. Proposed mechanism for the hydroarylation of **4**.

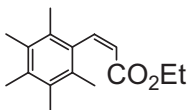
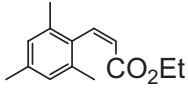
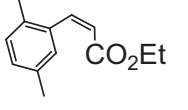
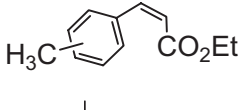
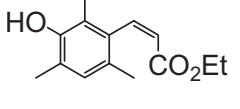
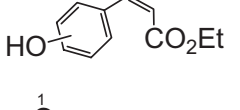
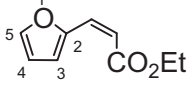
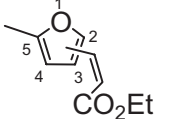
1.3.1.4.3 Scope and Limitations

The hydroarylation of aryl-substituted alkynes using activated AuCl₃ is fairly general, if electron-rich arenes are used as arylating compounds [2, 4]. Benzene or toluene do not react. Scheme 7 summarizes most of the results published on this subject. Cyclization reactions using AuCl₃ have been reported [8], but activated forms as shown above should lead to improved yields [4].



Scheme 7. Scope of the hydroarylation reaction with aryl-substituted alkynes. Conditions: 1.5 mol% AuCl_3 , 3.0 mol% AgSbF_6 , 10 equivalents arene, CH_3NO_2 , 50°C , 4 h. (GC yield/isolated yield); nd = not determined.

Table 2. Hydroarylation of acetylene carboxylic acid ester **4** by various arenes.^a

Entry	Arene (equiv.)	Co-catalyst	Time (h)	Temp (°C)	Product	Yield (%) ^b (Z:E) ^c
1	Pentamethylbenzene (3)	BF ₃ ·OEt ₂	14	50		98 (100:0)
2	Mesitylene (30)	BF ₃ ·OEt ₂	14	50		90 (100:0)
3	<i>p</i> -Xylene (15)	BF ₃ ·OEt ₂	14	50		55 (95:5)
4	Toluene (15)	BF ₃ ·OEt ₂	14	50		(15) (100:0) <i>o</i> : <i>p</i> = 60:40
5	2,4,6-Trimethylphenol (10)	BF ₃ ·OEt ₂	14	50		83 (100:0)
6	Phenol (3)	BF ₃ ·OEt ₂	14	50		(0)
7	Furan (20)	AgSbF ₆	3	40		82 (>99:1) ^d
8	2-Methylfuran (20)	AgSbF ₆	4	r.t.		(80) (Z, traces of the <i>E</i> -2-isomer are formed) 3 isomers (82:15:3) ^e

^a Conditions: 1 mol% Ph₃PAuCl, 1 mol% AgSbF₆ or 5 mol% BF₃·OEt₂, CH₃NO₂, excess arene

^b Isolated yields of purified products. GC Yields (determined with *n*-hexadecane as an internal standard) in parentheses

^c Determined by GC or NMR

^d GC of the crude product shows minor amounts of two other isomers and side products (according to GC–MS analysis hydroarylation products containing two furyl moieties or two alkenyl moieties, respectively)

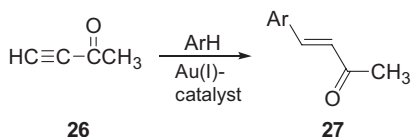
^e The product consists of 82 % Z-2 isomer, 15 % Z-4 isomer, and 3 % of a third isomer, probably the Z-3 isomer (this isomer was characterized only by GC–MS). Traces of a side product which, according to GC–MS analysis contains two methylfuryl moieties are formed

Internal aryl-substituted alkynes also undergo Au(III)-catalyzed hydroarylation with electron-rich alkynes (Table 1) [2, 4]. The reactivity of diphenylacetylene, however, is very low.

As delineated above, hydroarylation of electron-poor alkynes such as acetylene carboxylic acid ethyl ester **4** is best catalyzed by Au(I) complexes. In addition to the previously mentioned $\text{Ph}_3\text{PAuCl/BF}_3 \cdot \text{OEt}_2$, several other Au(I)-complexes have been shown to be active catalysts, if activation by silver salts or Lewis acids is ensured [2, 4]. Remarkably, the Au(I)-precursor LAuCl can be prepared in situ by reacting AuCl with a phosphorus ligand.

The scope and limitation of hydroarylation of acetylene carboxylic acid ester **4** using Au(I)-catalysis is revealed in Table 2. Electron-rich arenes participate well, but also furan and 2-methylfuran. *p*-Xylene leads to a 55 % yield, whereas an unacceptably low conversion results in the case of toluene.

The hydroarylation of such acetylenic ketones as 3-butyne-2-one **26** poses no problems. In these cases nearly complete *E*-selectivity was observed, because of isomerization of the kinetically formed *Z* compounds [2, 4]. Four different electron-rich arenes, ArH , were shown to react smoothly, affording products **27** in yields of 77–96 %.



Scheme 8. Hydroarylation of 3-butyne-2-one **26**.

In conclusion, Au(I) and Au(III) catalysts are well suited to the step- and atom-economical hydroarylation of alkynes. In general cationization is essential [2,4], which is now used in many other Au-catalyzed reactions. Previous work has shown that other metal catalysts such as Pd, In, and Sc salts are also active [3]. In some cases these catalysts are more effective (e.g. when benzene is used); in other cases less attractive (Pd-catalysis requires trifluoroacetic acid as solvent) [3a, b]. With gold catalysis, aqueous workup and neutralization are not necessary which is a substantial advantage. Recently, a similar gold-catalyzed process for the hydroarylation of electron-poor alkynes using $\text{AuCl}_3/3\text{AgOTf}$ (0.5–5 mol%) was published [9]. In contrast with our results, the authors favor a mechanism via aryl–gold intermediates.

Experimental

General Procedure for Hydroarylation of Aryl-substituted Alkynes (Small-scale Experiments)

Liquid Arenes

Stock solutions of AuCl_3 ($c = 0.015 \text{ M}$) and AgSbF_6 ($c = 0.030 \text{ M}$) in nitromethane were prepared. Each solution (0.90 mL) was added to a reaction flask under argon. An orange precipitate was observed. Arene (9.0 mmol) and alkyne

(0.90 mmol) (solid alkyne as a concentrated solution in nitromethane) were then added using syringes. The reaction mixture was stirred for 4 h at 50 °C. After cooling, 100 μ L *n*-hexadecane and 2 mL ethyl acetate were added. An aliquot (ca. 0.5 mL) was taken and filtered through a small plug of silica gel (elution with ethyl acetate). The yield of hydroarylation product was determined by GC. The double bond structure was determined by ^1H NMR of the crude product after all volatiles had been removed under vacuum.

Solid Arenes

Solid arenes (9.0 mmol) were weighed into the reaction flask in air. The flask was then evacuated for several minutes and charged with argon (3 \times). Nitromethane (2 mL) was added. The Au- and Ag-solutions and the alkyne (0.90 mmol) were added rapidly, and the reaction mixture was stirred at 50 °C for 4 h. Workup was conducted as described above.

General Procedure for Hydroarylation of Aryl-substituted Alkynes (Large-scale Experiments)

Liquid Arenes

AuCl_3 (45.5 mg, 0.150 mmol) and AgSbF_6 (103 mg, 0.300 mmol) were weighed into a 100-mL Schlenk-flask under argon. Nitromethane (20 mL) was added. The arene (100 mmol) and the alkyne (10 mmol; solid alkyne as a concentrated solution in nitromethane) were added, and the reaction mixture was stirred for 4 h at 50 °C. After cooling, the solvent and excess arene were removed under vacuum. The residue was purified by column chromatography (silica gel, hexanes–ethyl acetate). After removal of all the volatiles, an oil remained which was further purified by distillation under diffusion pump vacuum ($<10^{-3}$ mbar).

Solid Arenes (2,4,6-Trimethylphenol)

2,4,6-Trimethylphenol (13.62 g, 100.0 mmol) was weighed into a 100-mL Schlenk-flask in air. The flask was then evacuated for several minutes and charged with argon (3 \times). Nitromethane (20 mL) was added. Solutions of 45.5 mg AuCl_3 (0.150 mmol) and 103 mg AgSbF_6 (0.300 mmol) in 8.0 mL nitromethane and the alkyne (10 mmol, solid alkyne as a concentrated solution in nitromethane) were added rapidly. The reaction mixture was stirred at 50 °C for 4 h. After cooling, the solvent was removed under vacuum. Excess 2,4,6-trimethylphenol was removed by sublimation under vacuum (ca. 10^{-2} mbar) at 80 °C. The further workup procedure was the same as described above.

General Procedure for Hydroarylation of 4 by 1 with *in-situ* Prepared Gold Complexes

AuCl (6.28 mg, 0.027 mmol) and a (solid) phosphorus ligand (0.027 mmol) were weighed into a reaction flask in air. The flask was evacuated for several minutes and charged with argon (3 \times). Nitromethane (2 mL) was added. Liquid phosphorus ligands (0.027 mmol) were now added (either with microliter syringes or as stock solutions in nitromethane). Yellow suspensions were obtained which became

clear colorless solutions within a few minutes of stirring. Stock solution of $\text{BF}_3 \cdot \text{OEt}_2$ in nitromethane ($c = 0.027 \text{ M}$, 1.0 mL) was added. Finally, mesitylene **1** (0.38 mL, 2.7 mmol) and acetylene carboxylic acid ester **4** (92 μL , 0.90 mmol) were added rapidly. The reaction mixture was stirred for 14 h at 50 °C. After cooling, 100 μL *n*-hexadecane and 2 mL ethyl acetate were added. An aliquot (ca. 0.5 mL) was taken and filtered through a small plug of silica gel (elution with ethyl acetate). The yields of **5** and **6** were determined by GC.

General Procedure for Hydroarylation of Alkynes **4** and 3-Butyn-2-one **26** by Different Arenes with Ph_3PAuCl under Optimized Conditions (Small-scale Experiments)

Liquid Arenes

Ph_3PAuCl (4.45 mg, 0.009 mmol) was weighed into a reaction flask in air. The flask was then evacuated for several minutes and charged with argon (3 \times). Nitromethane (2.0 mL) was added, and then the co-catalyst (either 1.5 mL of a 0.030 M solution of $\text{BF}_3 \cdot \text{OEt}_2$ in nitromethane or 0.90 mL of a 0.010 M solution of AgSbF_6 in the same solvent) was added. Finally, the flask was charged with the arene (excess) and the alkyne (0.90 mmol). The reaction mixture was stirred at the temperature and for the time given in Table 2. Workup was conducted as described above.

Solid Arenes

Solid arenes and the gold catalyst were weighed into the flask in air. The flask was then evacuated for several minutes and charged with argon (3 \times). Nitromethane (2.0 mL) was added. A solution of the co-catalyst and the alkyne was then added. The further procedure was as described above for liquid arenes.

General Procedure for Hydroarylation of Alkynes **4** and 3-Butyn-2-one **26** by Different Arenes with Ph_3PAuCl under Optimized Conditions (Large-scale Experiments)

Liquid Arenes

Ph_3PAuCl (24.7 mg, 0.0500 mmol) and (where applicable, see Table 2) AgSbF_6 (17.2 mg, 0.0500 mmol) were weighed in a 100-mL Schlenk-flask under argon. Nitromethane (5.0 mL) and (where applicable, see Table 2) (32 μL , 0.25 mmol) $\text{BF}_3 \cdot \text{OEt}_2$ were added and the arene (excess) and alkyne (5.0 mmol) were then added rapidly. The reaction mixture was stirred for the time and at the temperature given in the Table 2. After cooling, the solvent was removed under reduced pressure, and the remaining residue was purified by column chromatography (silica gel, hexanes–ethyl acetate).

Solid Arenes

Solid arenes were weighed into a 100-mL Schlenk-flask in air with Ph_3PAuCl (24.7 mg, 0.0500 mmol). The flask was then evacuated for several minutes and charged with argon (3 \times). Nitromethane (20–35 mL) was added. Finally, $\text{BF}_3 \cdot \text{OEt}_2$ (32 μL , 0.25 mmol) and the alkyne (5.0 mmol) were added. The reaction mixture

was stirred for the time and at the temperature given in the Table 2. The workup procedure was as described above for liquid arenes.

1.3.2

Alkylation and Vinylation via Intermediary Transition Metal σ -Complexes of Arenes

1.3.2.1 Ruthenium-catalyzed ortho-Activation of Carbonyl-substituted Arenes

Fumitoshi Kakiuchi and Shinji Murai

1.3.2.1.1 Introduction and Fundamental Examples

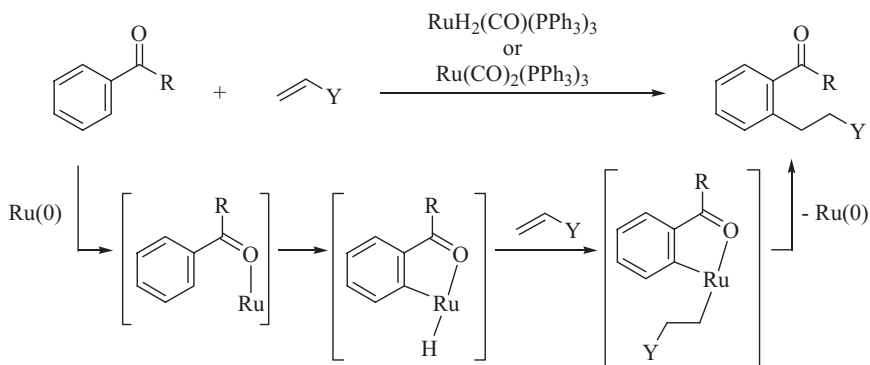
Since the early 1960s, carbon–hydrogen bond cleavage has been an attractive research subject for organometallic and organic chemists [1, 2] and many studies have been reported. These studies have usually focused on isolation and characterization of highly reactive H–M–R species formed by an oxidative addition of C–H bonds to transition metals, and on theoretical and kinetic considerations of the C–H bond-cleavage step. Catalytic C–H bond transformation such as conversion of C–H bonds to C–C bonds is one of the most challenging research subjects. Until the early 1990s much effort had been devoted to this subject but only a limited number of examples of catalytic C–H bond transformations had been reported. In 1993 the first example of highly efficient, selective catalytic addition of C–H bonds in aromatic ketones to olefins was reported [3]. This finding was epochal in this area. The situation in catalytic C–H bond transformation changed dramatically. Use of C–H bonds has since become a highly powerful, reliable synthetic tool in organic chemistry.

Among C–H bond transformations, one of the most important goals has been to achieve the one-step addition of a C–H bond across the double bond of an olefin (C–H/olefin coupling) and across the triple bond of an acetylene (C–H/acetylene coupling), because carbon–carbon bond formation is a highly important reaction in organic synthesis. This transformation must be highly efficient, selective, and widely applicable for the purpose of an organic synthesis. To achieve high regioselectivity chelation-assistance is often used in catalytic C–H bond transformation.

The pioneering work in catalytic additions of C–H bonds to olefins by means of chelation-assistance was the ethylation of phenols catalyzed by a ruthenium phosphite complex [4]. Later, the zirconium-catalyzed α -selective alkylation of α -picolines with olefins was reported [5]. In these cases, coordination of a heteroatom is the key to achieving high regioselectivity. Although these results were quite promising for catalytic C–H bond transformation, generality and efficiency were insufficient for use as a synthetic tool in organic synthesis.

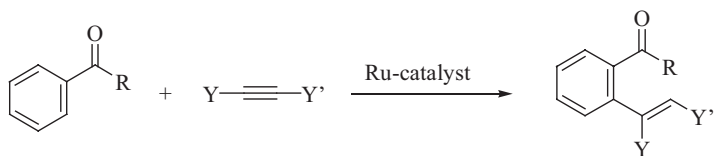
In 1993, Murai found that the ortho-selective alkylation of aromatic ketones with olefins with a ruthenium catalyst such as $\text{Ru}(\text{H})_2(\text{CO})(\text{PPh}_3)_3$ or $\text{Ru}(\text{CO})_2(\text{PPh}_3)_3$ proceeded with high efficiency and selectivity (Scheme 1) [3]. One of the most important factors in the success of this coupling reaction involves chelation-assistance by an oxygen of the ketone carbonyl group. Thus, coordination of the oxygen atom to the ruthenium brings the ruthenium center closer to the C–H bond and

stabilizes the C–Ru–H species formed by oxidative addition to the ruthenium of an ortho C–H bond in aromatic ketones. In addition, use of the chelation-assistance leads to high regioselectivity, an essential factor in organic synthesis.



Scheme 1. The proposed reaction pathway of the ruthenium-catalyzed C–H/olefin coupling by means of the chelation-assistance.

This C–H/olefin coupling can be extended to coupling with acetylenes [6]. The reaction of aromatic ketones with internal acetylenes gives the ortho alkenylated product in high yield (Scheme 2), but reaction with terminal acetylenes does not afford the coupling product. With terminal acetylenes, dimerization of acetylenes occurs as a predominant reaction.



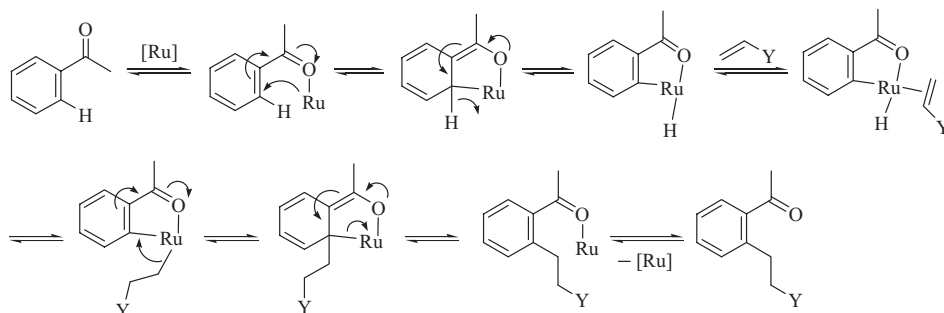
Scheme 2. Ruthenium-catalyzed C–H/acetylene coupling.

This chelation-assisted C–H/olefin and C–H/acetylene coupling can be applied to a variety of aromatic compounds with a directing group such as ester, aldehyde, imine, azo, oxazolyl, pyridyl, and nitrile [7]. In this section, we describe the coupling reactions of aromatic carbonyl compounds with olefins using a transition metal catalyst.

1.3.2.1.2 Mechanism

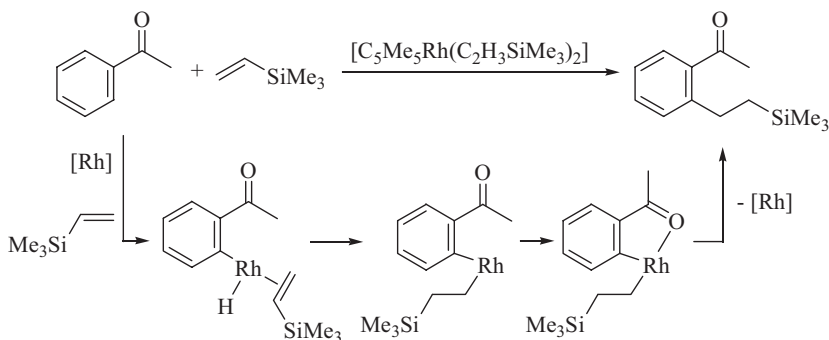
In general, it has been suggested that oxidative addition of a C–H bond to a transition metal giving a C–M–H species and reductive elimination leading to C–C bond formation proceed via a concerted pathway. Ruthenium-catalyzed chelation-assisted coupling of aromatic compounds with olefins, C–H bond cleavage, and C–C bond formation are, however, believed to proceed stepwise through the pathway shown in Scheme 3. Therefore, the C–H bond cleavage occurs as a result of

nucleophilic attack of low-valent ruthenium on the ortho carbon of aromatic compounds followed by migration of the ortho hydrogen to the ruthenium center; C–C bond formation proceeds as a result of attack of the alkyl group on the ruthenium atom [8]. The most important feature of this coupling reaction is that each step before the reductive elimination is in rapid equilibrium – thus, C–H bond cleavage is not rate-determining and C–C bond formation (reductive elimination) is rate-determining [8]. Murai proposed this unusual pathway for ruthenium-catalyzed C–H/olefin coupling on the basis of experimental evidence [8]. Later, Morokuma and Koga revealed the validity of Murai’s proposed pathway on the basis of *ab initio* theoretical calculation [9].



Scheme 3. Proposed stepwise pathway for the ruthenium-catalyzed C–H/olefin coupling.

In $(\text{C}_5\text{Me}_5)\text{Rh}(\text{C}_2\text{H}_3\text{SiMe}_3)_2$ -catalyzed C–H/olefin coupling the effect of the coordination of the ketone carbonyl is different from that in the ruthenium-catalyzed reaction [10]. In the rhodium-catalyzed reaction all C–H bonds on the aromatic ring are cleaved by the rhodium complex without coordination of the ketone carbonyl. Thus, C–H bond cleavage and addition of Rh–H to olefins proceed without coordination of the ketone carbonyl. After addition of the Rh–H species to the olefin, a coordinatively unsaturated Rh(aryl)(alkyl) species should be formed. Coordination of the ketone carbonyl group to the vacant site on the rhodium atom leads



Scheme 4. The reaction pathway of the $(\text{C}_5\text{Me}_5)\text{Rh}(\text{C}_2\text{H}_3\text{SiMe}_3)_2$ -catalyzed reaction of aromatic ketones with olefins.

to the 18-electron rhodium species. Coordination of the ketone carbonyl facilitates the reductive elimination.

Although there are several examples of transition metal-catalyzed addition of C–H bonds to acetylenes, there is neither experimental evidence nor theoretical consideration in respect of a reaction mechanism for C–H/acetylene coupling. This coupling reaction is believed to proceed through a pathway similar to that proposed for C–H/olefin coupling.

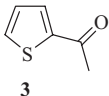

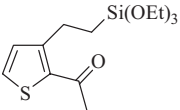
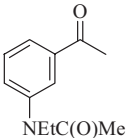

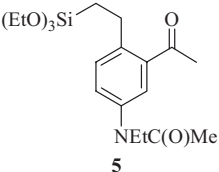
1.3.2.1.3 Scope and Limitations

The ruthenium-catalyzed addition of C–H bonds in aromatic ketones to olefins can be applied to a variety of ketones, for example acetophenones, naphthyl ketones, and heteroaromatic ketones. Representative examples are shown in the Table 1. Terminal olefins such as vinylsilanes, allylsilanes, styrenes, *tert*-butylethylene, and 1-hexene are applicable to this C–H/olefin coupling reaction. Some internal olefins, for example cyclopentene and norbornene are effective in this alkylation. The reaction of 2-acetonaphthone **1** provides the 1-alkylation product **2** selectively. Alkylations of heteroaromatic ketones such as acyl thiophenes **3**, acyl furans, and acyl pyrroles proceed with high yields. In the reaction of di- and tri-substituted aromatic ketones such as **4**, which have two different ortho positions, C–C bond formation occurs at the less congested ortho position. Interestingly, in the reaction of *m*-methoxy- and *m*-fluoroacetophenones C–C bond formation occurs at the congested ortho position (2'-position).

Table 1. Examples of the coupling of aromatic ketones with olefins.

Aromatic ketone	Olefin	Catalyst	Product	Yield (%)	Ref.
		A		97	3,7,8
		A		89	3,7,8
		A		88	3,7,8

Table 1. Continued

Aromatic ketone	Olefin	Catalyst	Product	Yield (%)	Ref.
 3	 Si(OEt) ₃	A		93	3,7,8
 4	 Si(OEt) ₃	A	 5	92	7,8

note: A: Ru(H)₂(CO)(PPh₃)₃

Several related examples of transition metal-catalyzed addition of C–H bonds in ketones to olefins have been reported (Table 2) [11–14]. The alkylation of diterpenoid **6** with olefins giving **7** proceeds with the aid of Ru(H)₂(CO)(PPh₃)₃ (**A**) or Ru(CO)₂(PPh₃)₃ (**B**) as catalyst [11]. Ruthenium complex **C**, Ru(H)₂(H₂)(CO)(PCy₃)₂, has catalytic activity in the reaction of benzophenone with ethylene at room temperature [12]. The alkylation of phenyl 3-pyridyl ketone **8** proceeds with **A** as catalyst [13]. Alkylation occurs selectively at the pyridine ring. Application of this C–H/olefin coupling to polymer chemistry using α,ω -dienes such as 1,1,3,3-tetramethyl-1,3-divinyldisiloxane **11** has been reported [14].

Table 2. Examples of couplings of aromatic ketones with olefins using transition metal catalysts.

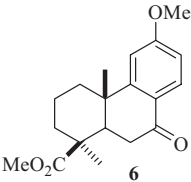
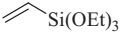
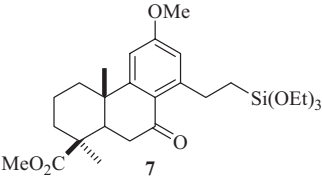
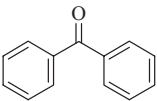
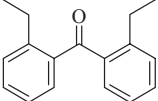
Aromatic ketone	Olefin	Catalyst	Product	Yield (%)	Ref.
 6	 Si(OEt) ₃	B	 7	100	11
	=	C		96	12

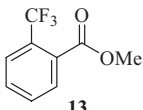
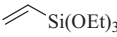
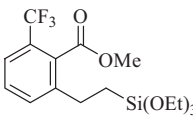
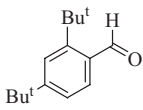
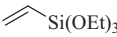
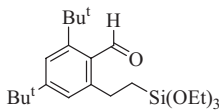
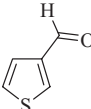
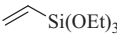
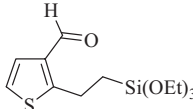
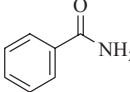

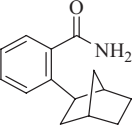
Table 2. Continued

Aromatic ketone	Olefin	Catalyst	Product	Yield (%)	Ref.
		D		99	10
		A		48	13
		A		85	14

note: A: $\text{Ru}(\text{H})_2(\text{CO})(\text{PPh}_3)_3$; B: $\text{Ru}(\text{CO})_2(\text{PPh}_3)_3$; C: $\text{Ru}(\text{H})_2(\text{H}_2)_2(\text{PCy}_3)_2$; D: $(\text{C}_5\text{Me}_5)\text{Rh}(\text{C}_2\text{H}_3\text{SiMe}_3)_2$

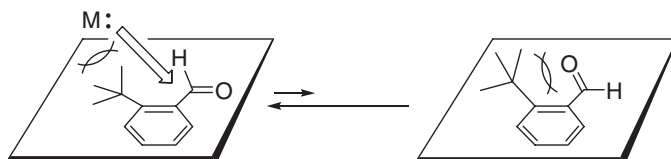
Chelation-assisted C–H/olefin coupling is also applicable to other aromatic carbonyl compounds (Table 3) [7]. For aromatic esters, electron-withdrawing groups such as CF_3 (**13**) and CN facilitate the C–H/olefin coupling reaction. In this alkylation, trimethylvinylsilane is more reactive (100 % yield in 1 h) than triethoxyvinylsilane (97 % yield in 24 h) [15]. In general, aldehydes are more reactive substrates towards nucleophilic reactions than ketones and esters. When aromatic aldehydes are exposed to low-valent transition metal complexes, a formyl group is attacked by the metal. Thus, several reactions such as decarbonylation of aldehydes and hydroacylations of olefins and acetylenes occur. To prevent nucleophilic attack on an aldehyde carbonyl group by a low-valent transition metal complex, two proposals have been made. One is steric effect (hypothesis A in Scheme 5), and the other is electronic effect (hypothesis B in Scheme 5). Reaction of benzaldehyde **14**, with a bulky substituent ortho to the formyl group, with an olefin provides the alkylation product **15** in good yield. Thiophenecarboxaldehyde **16** also reacts with an olefin to give alkylation product **17**. These results indicate that the hypotheses shown in Scheme 5 appears to operate in the alkylation of aromatic aldehydes. An amide carbonyl group can also function as a directing group. In this case, an iridium complex, $\text{Ir}(\text{C}_5\text{H}_5)((R)\text{-biphemp})$ (biphemp = 2,2'-bis(diphenylphosphino)-6,6'-dimethyl-1,1'-biphenyl), has catalytic activity [17]. This reaction gives the optically active alkylation products in moderate yields with high enantiomeric excess.

Table 3. Examples of coupling reactions of aromatic compounds with olefins.

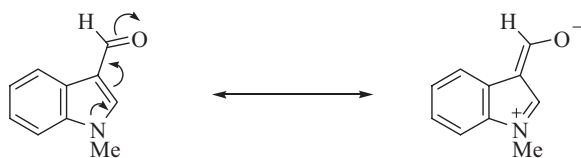
Aromatic ketone	Olefin	Catalyst	Product	Yield (%)	Ref.
 13	 Si(OEt) ₃	A	 Si(OEt) ₃	97	15
 14	 Si(OEt) ₃	A	 Si(OEt) ₃	69	16
 16	 Si(OEt) ₃	A	 Si(OEt) ₃	52	16
		E		35 87ee	17

note E: [Ir(C₅H₅)/(*R*)-biphep]

hypothesis A

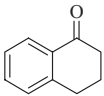
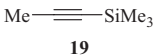
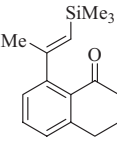
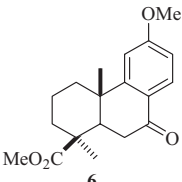
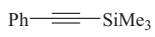
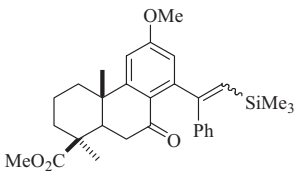
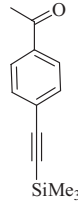
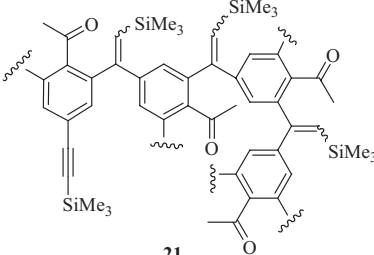
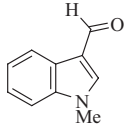
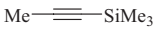
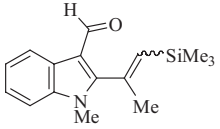


hypothesis B

**Scheme 5.** Hypothesis A: suppression of the reactivity of the formyl group by steric effects; hypothesis B: suppression of the reactivity of the formyl group by electronic effects.

Acetylenes can also be used in ruthenium-catalyzed C–H bond transformations. Selected results are listed in Table 4. The C–H bond of α -tetralone **18**, one of the most reactive ketones in the couplings with olefins, undergoes addition to the triple bond of 1-trimethylsilyl-1-propyne **19** with complete regioselectivity and stereoselectivity[6]. This indicates that the addition of a Ru–H (or, less likely, a Ru–C) bond to the acetylene proceeds in syn fashion. This C–H/acetylene coupling provides highly congested trisubstituted olefins in high yields. Alkenylation of **6** also occurs. Self-polymerization of **20** leads to polymer **21** in high yield. Hypothesis B in Scheme 5 is also effective for the alkenylation of C–H bonds with acetylenes.

Table 4. Examples of the coupling of aromatic ketones with acetylenes.

Aromatic ketone	Acetylene	Catalyst	Product	Yield (%)	Ref.
 18	 19	A		83 (<i>E</i> only)	6
 6		A		94 (<i>E</i> : <i>Z</i> = 50:50)	18
 20		A + styrene	 21	79	19
		A		42 (<i>E</i> : <i>Z</i> = 85:15)	16

Experimental

8-(2-Triethoxysilanylethyl)-3,4-dihydro-2H-naphthalen-1-one [8, 20]

Apparatus consisting of a 100-mL two-necked round-bottomed flask, a reflux condenser connected to a vacuum/N₂ line, an inlet tube sealed with a rubber septum, and a magnetic stirring bar was evacuated then flushed with nitrogen. This cycle was repeated four times. The apparatus was flame-dried under a flow of nitrogen, and then cooled to room temperature under a nitrogen atmosphere. Carbonyldihydridotris(triphenylphosphine)ruthenium(II), Ru(H)₂(CO)(PPh₃)₃, (0.918 g, 1.00 mmol) was placed in the flask under a slow flow of nitrogen. Addition of 20 mL toluene to the flask gave a suspension of white solid. To the suspension were added triethoxyvinylsilane (20.93 g, 110 mmol) and α -tetralone **18** (14.62 g, 100 mmol). The resulting mixture containing the white solids was heated under reflux. After heating for 30 min, the reaction mixture was cooled to room temperature. Volatile materials (toluene and triethoxyvinylsilane) were removed under reduced pressure. Distillation of the residue under reduced pressure gave 31–32.5 g (92–96 % yields) 8-(2-trimethylsilanylethyl)-3,4-dihydro-2H-naphthalen-1-one as a pale yellow liquid, b.p. 133–135 °C/0.2 mmHg. ¹H NMR (270 MHz, CDCl₃) 0.96–1.02 (c, 2 H, SiCH₂), 1.26 (t, *J* = 7.02 Hz, 9 H, CH₃), 2.07 (quint, *J* = 6.48 Hz, 2 H, CH₂CH₂CH₂), 2.64 (t, *J* = 6.48 Hz, 2 H, ArCH₂), 2.95 (t, *J* = 6.48 Hz, 2 H, C(O)CH₂), 3.10–3.16 (c, 2 H, ArCH₂CH₂Si), 3.88 (q, *J* = 7.02 Hz, 6 H, OCH₂), 7.09 (d, *J* = 7.56 Hz, 1 H, ArH), 7.14 (d, *J* = 7.56 Hz, 1 H, ArH), 7.33 (t, *J* = 7.56 Hz, 1 H, ArH); ¹³C NMR (67.5 Hz, CDCl₃) 12.11, 18.06, 22.68, 28.41, 30.82, 40.79, 58.01, 126.56, 128.99, 130.17, 132.15, 145.48, 147.78, 199.28.

8-(1-Methyl-2-trimethylsilanylviny)-3,4-dihydro-2H-naphthalen-1-one [6]

Apparatus consisting of a 10-mL two-necked flask equipped with a reflux condenser connected to a nitrogen line, a rubber septum, and a magnetic stirring bar was flame dried under a flow of nitrogen. In the flask were placed the ruthenium complex (0.110 g, 0.12 mmol), 3 mL toluene, α -tetralone **18** (0.292 g, 2 mmol), and 1-trimethylsilylpropyne **19** (0.448 g, 4 mmol). The resulting mixture was heated under reflux under a nitrogen atmosphere. After heating for 3 h the reaction mixture was cooled to room temperature. Volatile materials (toluene and 1-trimethylsilylpropyne) were removed under reduced pressure. Bulb-to-bulb distillation under reduced pressure gave 0.428 g (83 % yield) 8-(1-methyl-2-trimethylsilanylviny)-3,4-dihydro-2H-naphthalen-1-one as a pale yellow liquid, 110 °C/2 mmHg. ¹H NMR (CDCl₃) 0.02 (s, 9H, CH₃), 2.04 (s, 3H, CH₃), 2.10 (quint, *J* = 6.3 Hz, 2H, CH₂), 2.63 (t, *J* = 6.3 Hz, 2H, C(O)CH₂), 2.96 (t, *J* = 6.3 Hz, 2H, ArCH₂), 5.24 (s, 1H, CH=), 7.01 (d, *J* = 7.6 Hz, 1H, ArH), 7.14 (d, *J* = 7.6 Hz, 1H, ArH), 7.35 (t, *J* = 7.6 Hz, 1H, ArH); ¹³C NMR (CDCl₃) –0.29, 22.81, 23.02, 30.51, 40.20, 124.42, 127.33, 128.01, 129.26, 132.26, 144.87, 149.76, 157.65, 197.68.

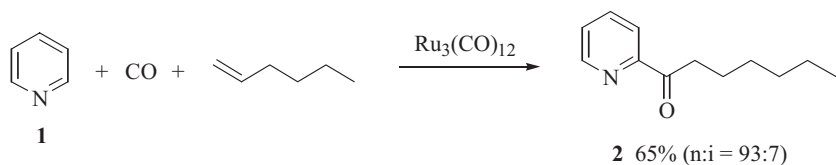
1.3.2.2 Ruthenium-Catalyzed α -Activation of Heteroarenes

Naoto Chatani

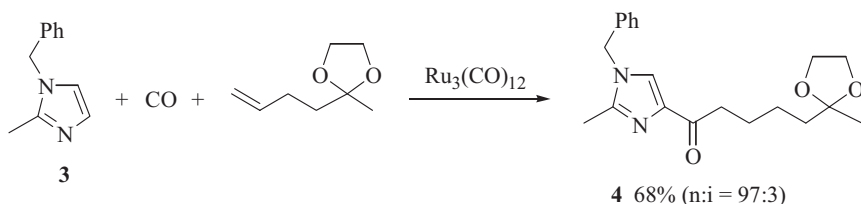
1.3.2.2.1 Introduction and Fundamental Examples

The selective functionalization of heterocycles is of particular importance, because of the ubiquity of these structures in natural products and pharmaceutical agents. Direct utilization of a C–H bond [1] of heterocycles is a promising method for the preparation of heterocycles because no pre-functionalization is required. Although Friedel–Crafts acylation is the most commonly used method for introduction of keto functionality on an aromatic ring, it is not often applicable to *N*-heteroarenes because of deactivation of the Lewis acids by the coordination of *N*-heteroarenes and the electron-deficient aromatic character of *N*-heteroarenes.

Direct selective acylation of pyridine was achieved by use of olefins and CO, with $\text{Ru}_3(\text{CO})_{12}$ as catalyst, as shown in Scheme 1 [2]. Reaction of pyridine **1** with CO and 1-hexene in the presence of $\text{Ru}_3(\text{CO})_{12}$ gave hexanoylpyridine **2** with a 93:7 ratio of linear and branched isomers. Use of 2-hexene or 3-hexene in place of 1-hexene also gave **2** with exactly the same linear/branched product ratio as in the reaction with 1-hexene.



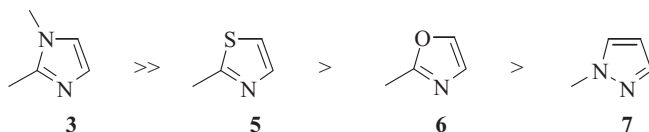
Scheme 1. C–H carbonylation at a C–H bond α to the nitrogen in pyridine; 1.3 mol% $\text{Ru}_3(\text{CO})_{12}$, no solvent, 10 atm, 150 °C, 16 h.



Scheme 2. C–H carbonylation at a C–H bond α to the nitrogen in imidazole; 4 mol-% $\text{Ru}_3(\text{CO})_{12}$, toluene, 20 atm, 160 °C, 20 h.

This type of C–H carbonylation is also feasible at C–H bonds in five-membered *N*-heteroaromatics, such as imidazoles **3** (Scheme 2), thiazoles **5**, oxazoles **6**, and pyrazoles **7** [3]. Functional group compatibility was extensively studied in the reaction of **3**, and it was found that a variety of functional groups, for example ketone, ester, cyano, acetal, *N,O*-acetal, ketal, and silyl groups, were tolerated under the reaction conditions, indicating that C–H carbonylation reactions have now reached a satisfactory level in organic synthesis. The reactivity of the five-membered *N*-heteroaromatics is significantly affected by the $\text{p}K_{\text{a}}$ of conjugate acid of the *N*-heteroaromatics.

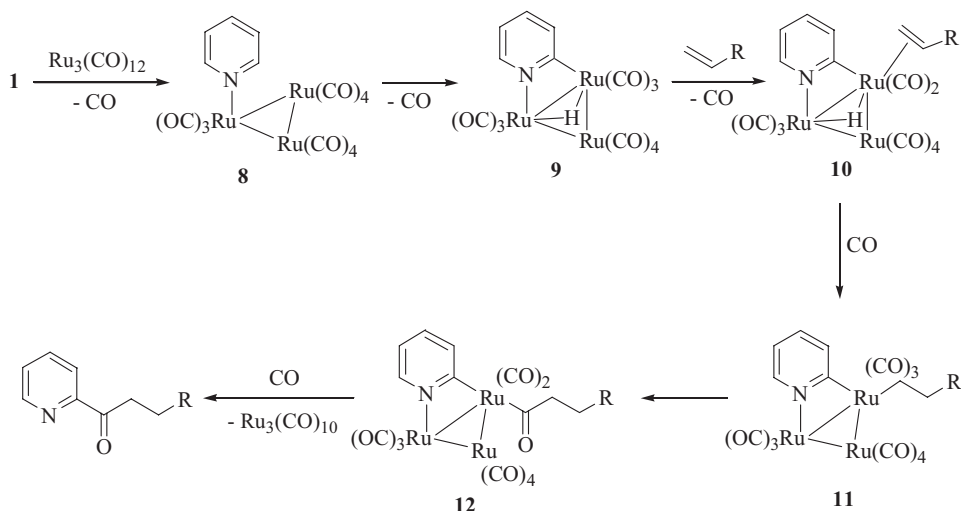
matic compounds, as shown in Scheme 3. Thus, the higher is the pK_a , the greater the reactivity. This indicates that coordination of the substrates by the sp^2 nitrogen to the ruthenium center is a key step in C–H carbonylation of *N*-heteroaromatics. The substrates must compete with CO to coordinate with ruthenium. In fact, reaction of pyrazole **7**, which has the lowest pK_a among the substrates shown in Scheme 3, proceeded effectively only when the reaction was conducted under a lower pressure of CO (3 atm, 46 %: 20 atm, trace). This observation emphasizes the importance of coordination of a nitrogen to ruthenium for the reaction to proceed.



Scheme 3. Order of reactivity of five-membered *N*-heteroaromatics in C–H carbonylation.

1.3.2.2.2 Mechanism

A trinuclear ruthenium cluster **9**, formed by coordination of the pyridine nitrogen to the ruthenium catalyst then specific activation of a C–H bond next to the nitrogen, is proposed as the key catalytic species. In fact, **9** had catalytic activity in the reaction shown in Scheme 1. Coordination of the olefin to the ruthenium center in **9** leading to **10**, insertion of the olefin into an H–Ru bond leading to **11**, and CO insertion gives the acyl ruthenium complex **12**, which undergoes reductive elimination to give the final product, with Ru being regenerated (Scheme 4). Coordination of pyridine through the sp^2 nitrogen is important. In fact, the monophosphine complex, $Ru_3(CO)_{11}(PPh_3)$, was much less active than $Ru_3(CO)_{12}$, and the triphosphine complex, $Ru_3(CO)_9(PPh_3)_3$, had no catalytic activity.



Scheme 4. Proposed reaction mechanism.

1.3.2.2.3 Scope and Limitations

In addition to five- and six-membered *N*-heteroaromatics, other *N*-heterocyclic compounds have been found to serve as substrates for C–H carbonylation reactions. Benzoimidazole **13** reacted in the same way with CO and olefins in the presence of $\text{Ru}_3(\text{CO})_{12}$, but carbonylation occurred at the C–H bond β to the sp^2 nitrogen to give **14** (Table 1). The same relationship between reactivity and the $\text{p}K_{\text{a}}$ values of conjugate acids of heterocycles was also observed in the β carbonylation [4].

Table 1. Examples of the structural diversity of C–H carbonylation reactions (conditions are different in each reaction).

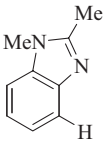

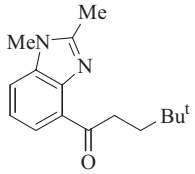
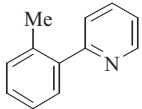
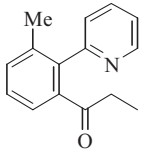
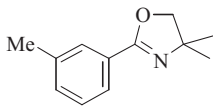
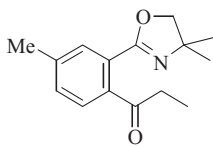
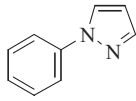
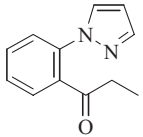
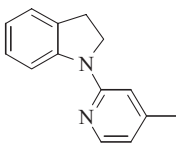
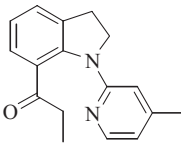
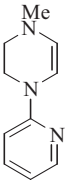
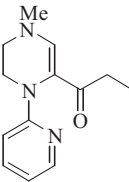
Starting materials	Olefins	Products	Yield (%)	Ref.
 <p>13</p>		 <p>14</p>	77	4
 <p>15</p>	$\text{H}_2\text{C}=\text{CH}_2$	 <p>16</p>	80	5
 <p>17</p>	$\text{H}_2\text{C}=\text{CH}_2$	 <p>18</p>	91	6
 <p>19</p>	$\text{H}_2\text{C}=\text{CH}_2$	 <p>20</p>	94	7

Table 1. Continued

Starting materials	Olefins	Products	Yield (%)	Ref.
 21	H ₂ C=CH ₂	 22	65	8
 23	H ₂ C=CH ₂	 24	85	9

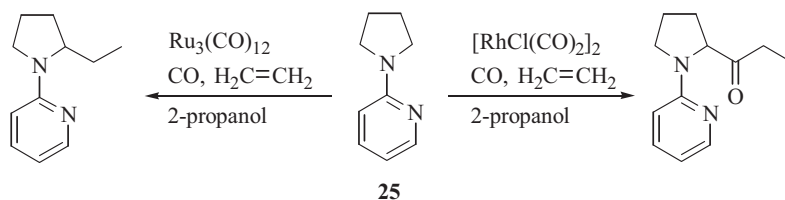
The 2-arylpyridine **15** did not undergo C–H carbonylation at the C–H bond in the pyridine ring, but instead at the ortho C–H bond (the C–H bond γ to the sp^2 nitrogen) in the aryl ring to give **16** [5]. This γ carbonylation was applicable to aryloxazolines and *N*-arylpyrazoles. Regioselective carbonylation occurred at the less hindered C–H bond when meta-substituted phenyloxazoline **17** was used as the substrate [6]. A pyrazole ring also functioned as the directing group, as in **19** [7].

Although examples are few, C–H carbonylation at C–H bonds δ to the sp^2 nitrogen was achieved when *N*-pyridylindoline **21** was used as the substrate [8]. The reaction is sensitive to solvent polarity. The choice of *N,N*-dimethylacetamide as solvent is crucial for the reaction to proceed efficiently. In the γ - and δ -carbonylation, only ethylene works effectively as coupling partner.

C–H carbonylation catalyzed by $Ru_3(CO)_{12}$ is applicable to olefinic C–H bonds, as in **23** [9].

A high-throughput procedure using a mass spectrometric labeling strategy for examining applicable substrates in C–H carbonylation catalyzed by $Ru_3(CO)_{12}$ has recently been reported [10].

The directing group promoted C–H activation reaction is applicable to sp^3 C–H bonds adjacent to the nitrogen in alkylamines, as shown in Scheme 5. Alkylation occurred when reaction of **25** with CO and ethylene was conducted in the presence of $Ru_3(CO)_{12}$ as catalyst [11]. On the other hand, the use of a rhodium complex as catalyst resulted in C–H carbonylation [12].



Scheme 5. C–H carbonylation and alkylation at the sp^3 C–H bond α to the nitrogen.

Experimental

1-(1-Benzyl-2-methyl-1H-imidazol-4-yl)-5-(2-methyl-[1,3]dioxolan-2-yl)-pentan-1-one (4)

$\text{Ru}_3(\text{CO})_{12}$ (25 mg, 0.04 mmol), 1-benzyl-2-methyl-1H-imidazole (3) (172 mg, 1 mmol), 2-but-3-enyl-2-methyl[1,3]dioxolane (568 mg, 4 mmol), and toluene (3 mL) were placed in a 50-mL stainless-steel autoclave. The system was flushed with 10 atm CO three times, then pressurized with CO to 20 atm, then immersed in an oil bath at 160 °C. After 20 h, it was removed from the oil bath and left to cool for ca. 1 h; the gases were then released. After evaporation, the resulting residue was subjected to column chromatography on silica gel with hexane–EtOAc as eluent to give 4 (233 mg, 68 % yield) as a colorless oil. An analytical sample was obtained by bulb-to-bulb distillation. Colorless oil; R_F = 0.20 (EtOAc); ^1H NMR (CDCl_3) δ 1.30 (s, 3H, CH_3C), 1.39–1.54, 1.60–1.80 (m, 6H, CH_2), 2.37 (s, 3H, 2- CH_3), 2.94 (t, J = 7.6 Hz, 2H, $\text{CH}_2\text{C}(\text{O})$), 3.83–3.96 (m, 4H, CH_2O), 5.06 (s, 2H, CH_2N), 7.00–7.13, 7.28–7.42 (m, 5H, Ph), 7.51 (s, 1H, 5-H); ^{13}C NMR (CDCl_3) δ 13.19 (2- CH_3), 23.70, 23.83, 24.30, 38.60, 38.96 (CH_2 , CH_3), 50.33 (CH_2N), 64.53 (CH_2O), 110.01 (CH_3), 124.37 (5-C), 126.90, 128.37, 129.11, 134.99 (Ph), 140.31 (4-C), 145.62 (2-C), 196.17 (CO); IR (neat) 3130 w, 2930 s, 2878 s, 2646 w, 2198 w, 1812 s, 1667 s, 1539 s, 1499 m, 1457 s, 1414 s, 1375 s, 1312 m, 1206 s, 1163 s, 1061 s, 944 m, 853 m, 790 m, 730 m, 698 s, 668 m, 640 m; MS, m/z (rel. intensity) 342 (M^+ , 3), 228 (28), 227 (20), 215 (14), 214 (81), 199 (36), 172 (14), 91 (100), 87 (78). Anal. Calcd for $\text{C}_{20}\text{H}_{26}\text{N}_2\text{O}_3$: C, 70.15; H, 7.65; N, 8.18. Found: C, 70.22; H, 7.55; N, 8.22.

1.3.2.3 Ruthenium(II)- and Iridium(III)-catalyzed Addition of Aromatic C–H Bonds to Olefins

T. Brent Gunnoe and Roy A. Periana

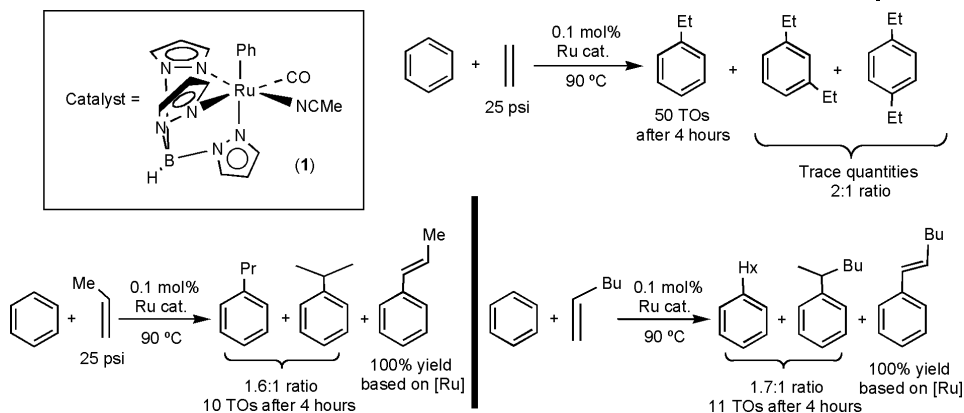
1.3.2.3.1 Introduction and Fundamental Examples

Ru(II) Catalysts

Additions of aromatic C–H bonds across olefin double bonds (olefin hydroarylation) are catalyzed by the Ru(II) complex $\text{TpRu}(\text{CO})(\text{NCMe})(\text{Ph})$ (**1**) (Tp = hydrido-tris(pyrazolyl)borate; Scheme 1) [1, 2]. The reactions proceed at moderate temperature (90 °C) with relatively low olefin concentrations. For the catalytic hydrophenylation of ethylene, approximately 50 turnovers are obtained after 4 h using 0.1 mol% of complex **1** in benzene and 25 psig ethylene. After 24 h, approximately 80 turnovers are observed after which catalytic activity ceases. At low ethylene pressures (<60 psig), ethylbenzene is the primary product with traces of 1,3- and 1,4-diethylbenzene observed. Increasing olefin pressure reduces the rate of catalysis. For example, at 250 psig ethylene pressure only 5 equiv. ethylbenzene are produced (per equiv. catalyst) after 4 h reaction at 90 °C. For reactions incorporating 1-hexene greater catalytic activity is observed with increasing olefin concentration up to approximately 60 equiv. olefin (based on Ru). Increasing the 1-hexene/catalyst ratio above 60:1 results in a decrease in the rate of catalysis. Hydrophenylation reactions of α -olefins (e.g. propene or 1-hexene) result in reduced catalytic activity compared with the hydrophenylation of ethylene. In addition, stoichiometric production of *trans*- β -alkyl styrenes results in termination of the catalysis after approximately 10 to 12 turnovers (Scheme 1). In the hydrophenylation of ethylene formation of styrene is not detected at low ethylene pressures; at higher ethylene pressure (250 psig), however, traces of styrene are produced with a small amount of butylbenzene, because of a second ethylene insertion step. The hydrophenylation of ethylbenzene produces 1,3-diethylbenzene and 1,4-diethylbenzene in an approximately 2:1 ratio.

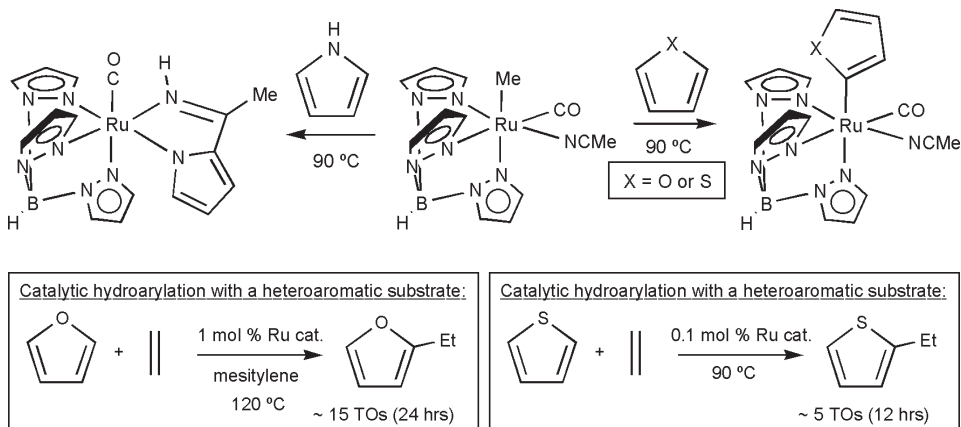
These catalytic reactions provide a unique pathway for addition of aromatic C–H bonds across C=C bonds. In contrast with Friedel–Crafts catalysts for olefin hydroarylation, the Ru-catalyzed hydrophenylation reactions of α -olefins selectively produce linear alkyl arenes rather than branched products. Although the selectivity is mild, the formation of anti-Markovnikov products is a unique feature of the Ru(II) and Ir(III) catalysts discussed herein. Typically, the preferred route for incorporation of long-chain linear alkyl groups into aromatic substrates is Friedel–Crafts acylation then Clemmensen reduction, and the catalysts described herein provide a more direct route to linear alkyl arenes.

$\text{TpRu}(\text{CO})(\text{NCMe})(\text{Me})$ reacts with thiophene and furan to initiate stoichiometric C–H activation at the 2-position (Scheme 2). After both reactions the 2-aryl products have been isolated and fully characterized [3]. Extension of these stoichiometric reactions to catalytic transformations has been demonstrated for furan or thiophene and ethylene. Heating a combination of 1 mol% $\text{TpRu}(\text{CO})(\text{NCMe})$ (2-furyl) in furan and mesitylene under 10–40 psig ethylene results in catalytic pro-



Scheme 1. $\text{TpRu(CO)(NCMe)(Ph)}$ catalyzes the hydroarylation of olefins (Pr = propyl, Hx = hexyl, Bu = butyl).

duction of 2-ethylfuran (Scheme 2). In addition, 0.1 mol% TpRu(CO)(NCMe) (2-thienyl) in thiophene under 40 psig ethylene pressure at 90 °C produces 2-ethylthiophene with five catalytic turnovers after 12 h. Pyrrole is also activated on reaction with $\text{TpRu(CO)(NCMe)(Me)}$, although C–C bond formation with the acetonitrile ligand occurs to produce a stable metallacycle (Scheme 2).



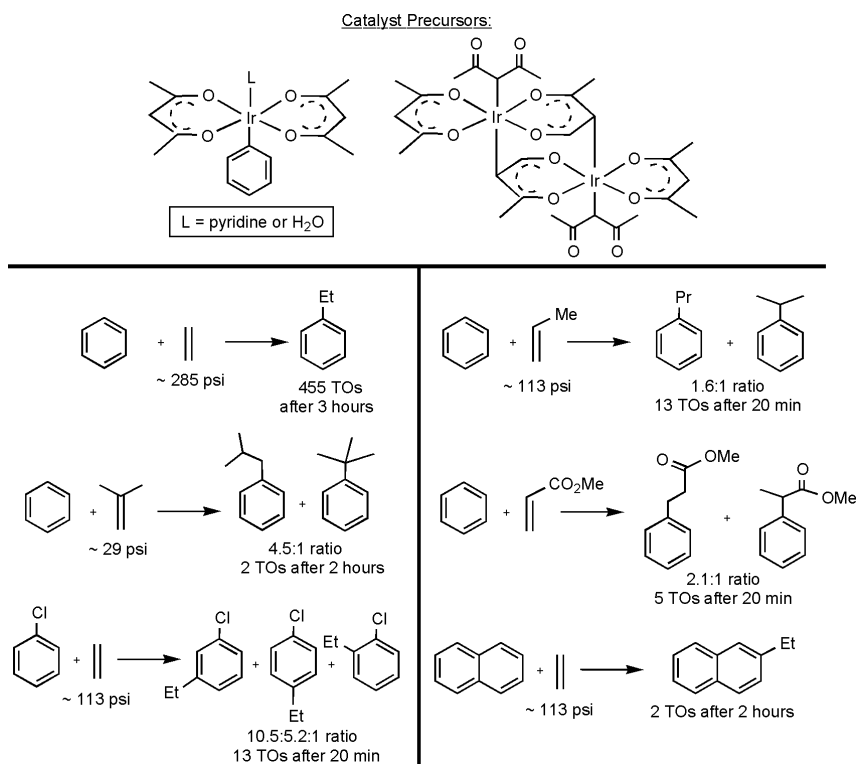
Scheme 2. Reactions of $\text{TpRu(CO)(NCMe)(Me)}$ with five-membered heteroaromatic substrates.

The Ru(II) catalysts currently used for olefin hydroarylation reactions are limited in terms of incorporation of substituents into the olefin substrate. For example, attempted hydrophenylation of isobutylene with $\text{TpRu(CO)(NCMe)(Ph)}$ as catalyst does not yield new organic products. In addition, extension of catalysis to hetero-functionalized olefins using the $\text{TpRu(CO)(NCMe)(aryl)}$ systems has not been successful. For electron-deficient olefins (e.g. styrene, methyl methacrylate, acrylonitrile) the TpRu(II) complexes initiate radical polymerization of the olefin in transformations that probably involve a Ru(III/II) redox change[4]. The

$\{\text{TpRu}^{\text{II}}(\text{CO})(\text{R})\}$ fragment reacts with olefins that bear electron-donating groups (e.g. ethyl vinyl ether or ethyl vinyl sulfide) to produce TpRu complexes that are not active in hydroarylation chemistry.

Ir(III) Catalysts

Ir(III) complexes can also be used to catalyze the hydroarylation of olefins [5, 6]. The catalyst precursors $(\text{acac-O},\text{O})_2\text{Ir}(\text{Ph})(\text{L})$ ($\text{L} = \text{pyridine}$ or H_2O) and $[\text{Ir}(\mu\text{-acac-O},\text{O},\text{C}^3)(\text{acac-O},\text{O})(\text{acac-C}^3)]_2$ have been reported and are depicted in Scheme 3, with representative catalytic reactions. Among these catalyst precursors, $(\text{acac-O},\text{O})_2\text{Ir}(\text{Ph})(\text{H}_2\text{O})$ has been demonstrated to be the most active system [5]. The linear-to-branched ratios observed for Ir(III) catalyzed reactions of α -olefins are remarkably similar to those obtained using $\text{TpRu}(\text{CO})(\text{NCMe})(\text{Ph})$. For example, hydrophenylation of propene using $[\text{Ir}(\mu\text{-acac-O},\text{O},\text{C}^3)(\text{acac-O},\text{O})(\text{acac-C}^3)]_2$ as catalyst produces a 1.6:1 ratio of linear propylbenzene to cumene (identical to the ratio observed using the Ru(II) catalyst). Similar to the $\text{TpRu}(\text{CO})(\text{NCMe})(\text{R})$ catalysts, the regioselectivity of hydroarylation of ethylene that incorporates monoalkyl arenes produces meta- and para-disubstituted alkyl arenes in approximately 2:1 ratio without observation of ortho-disubstituted products.



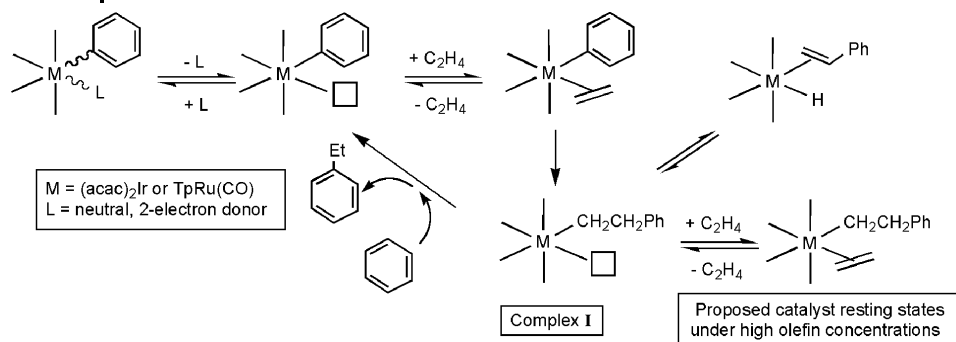
Scheme 3. Ir(III) catalyzed hydroarylation of olefins.

Advantages of the Ir(III)-catalyzed reactions over the Ru(II) systems include an increased number of turnovers as well as a more substantial range of olefins that are compatible with the catalyst. The hydrophenylation of ethylene using $[\text{Ir}(\mu\text{-acac-O,O,C}^3)(\text{acac-O,O})(\text{acac-C}^3)]_2$ as catalyst yields 455 turnovers after 3 hours at 180 °C whereas the $\text{TpRu}(\text{CO})(\text{NCMe})(\text{Ph})$ catalyst yields approximately 75 catalytic turnovers after 24 hours at 90 °C. The Ir(III) systems exhibit increased thermal stability relative to the $\text{TpRu}(\text{CO})(\text{R})(\text{NCMe})$ systems. In contrast to the Ru(II) catalytic systems, the hydrophenylation of α -olefins (e.g., propene or 1-hexene) catalyzed by Ir(III) does not yield observable quantities of β -alkyl styrenes. In addition, olefins that possess electron-withdrawing groups are compatible with the Ir(III) catalysts. For example, the hydrophenylation of methyl acrylate produces 3-phenylpropionic acid methyl ester and 2-phenylpropionic acid methyl ester (five turnovers) in a 2.1:1 ratio, and the hydrophenylation of styrene with 22 turnovers to produce 1,2-diphenylethane and 1,1-diphenylethane in a 45:1 ratio is observed. The Ir(III) catalysts exhibit reduced activity compared with the $\text{TpRu}(\text{II})$ systems requiring temperatures of approximately 180 °C {compared with approximately 90 °C for Ru(II)} to achieve sufficient rates of reaction.

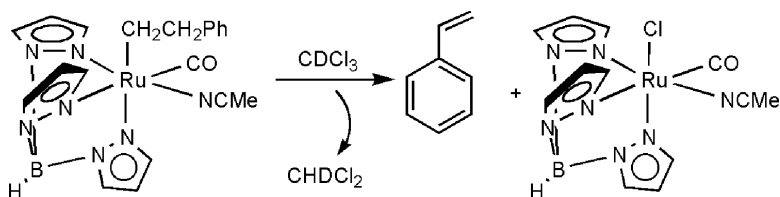
1.3.2.3.2 Mechanism

The mechanisms of catalytic hydroarylation of olefins by $\text{TpRu}(\text{CO})(\text{NCMe})(\text{Ph})$ and the Ir(III) systems shown in Schemes 1 and 3 have been studied both experimentally and computationally [2, 5, 7–9], and the proposed pathways are closely related. Catalyst precursors in both cases are coordinatively and electronically saturated 18-electron complexes with at least one labile ligand. Initial exchange between the labile ligand and olefin likely precedes olefin insertion (Scheme 4). Olefin insertion into a metal–aryl bond creates an open coordination site that can bind and activate the C–H bond of the aromatic substrate, and release of alkyl arene regenerates the active catalyst. The intermediates labeled **I** would be expected to undergo facile β -hydride elimination to produce metal hydride complexes with coordinated olefins. Osgaard and Goddard have calculated that the lack of production of olefinic products for hydroarylation reactions catalyzed by Ir(III) is because of the reversibility of the β -hydride elimination step [9]. Consistent with this proposal, experimental studies with $\text{TpRu}(\text{CO})(\text{NCMe})(\text{CH}_2\text{CH}_2\text{Ph})$ indicate that β -hydride elimination is kinetically facile and provide evidence for reversibility. For example, $\text{TpRu}(\text{CO})(\text{NCMe})(\text{CH}_2\text{CH}_2\text{Ph})$ rapidly produces free styrene, CHDCl_2 , and $\text{TpRu}(\text{CO})(\text{NCMe})(\text{Cl})$ on heating to 90 °C in CDCl_3 (Scheme 5). In the hydrophenylation of α -olefins by $\text{TpRu}(\text{CO})(\text{NCMe})(\text{Ph})$, formation of *trans*- β -alkyl styrenes is observed, and it has been proposed that the steric influence of the alkyl group raises the ground-state energy of $\text{TpRu}(\text{CO})(\text{H})(\eta^2\text{-trans-R})\text{HC}=\text{CH}(\text{Ph})$ relative to $\text{TpRu}(\text{CO})(\text{H})(\eta^2\text{-styrene})$ and increases the rate of dissociation [2].

At higher olefin concentrations the rate of catalysis, using either the Ru(II) or Ir(III) systems, decreases with increasing olefin concentration. For example, between 10 and 40 psig of ethylene pressure, the rate of hydrophenylation of ethyl-



Scheme 4. Proposed mechanisms for catalytic hydroarylation of olefins (benzene and ethylene depicted as substrates; note: the catalyst precursors for Ir(III) exhibit trans disposition of L and Ph).



Scheme 5. Evidence for facile β -hydride elimination is obtained upon heating TpRu(CO)(NCMe)(CH₂CH₂Ph) in CDCl₃.

ene catalyzed by TpRu(CO)(NCMe)(Ph) decreases. For analogous catalysis by [Ir(μ -acac-O,*O,C*³)(acac-O,*O*)(acac-C³)₂], the rate of catalysis increases with increasing ethylene pressure for ethylene/benzene ratios <0.2 whereas at ratios >0.2 the rate of ethylbenzene production decreases. These trends have been rationalized by invoking the trapping of catalytic intermediates after olefin insertion upon coordination of ethylene (Scheme 4). Thus, in order for the Ru(II) or Ir(III) systems to reenter the catalytic cycle, dissociation of dihapto-coordinated ethylene (or other olefin) must occur, and the reversible binding of ethylene results in inverse dependence of the rate of catalysis on olefin concentration. For the Ir(III) catalyst, lower concentrations of ethylene presumably shift the catalyst resting state such that olefin coordination is involved in the rate-determining step (or steps preceding the rate determining step) of the catalytic cycle, and a first-order dependence of catalytic rate on concentration of ethylene results.

1.3.2.3.3 Scope and Limitations

The Ru(II) and Ir(III) olefin hydroarylation catalysts have only recently been developed, and the scope and potential of these reactions have not been fully delineated. For example, the impact of altering ancillary ligand identity, metal oxidation

state and the identity of the metal center has not been extensively probed. At this stage, the $\text{TpRu}(\text{CO})(\text{NCMe})(\text{R})$ catalysts seem to be limited to hydroarylation reactions of ethylene and simple α -olefins. Incorporation of electron-donating groups or electron-withdrawing groups into the olefin results in side reactions that disrupt the olefin hydroarylation chemistry. The introduction of more than one alkyl group inhibits catalyst activity, presumably because of steric issues that restrict the olefin coordination which precedes the insertion/C–C bond-forming step. Benzene, monoalkyl arenes, thiophene, and furan can be used as aromatic substrates. Although the detailed mechanism has not been reported, use of pyrroles with N–H bonds is complicated by C–C coupling with acetonitrile, while also providing a potential new avenue for catalytic C–C bond formation (Scheme 2). Tolerance of functionality on the arenes (e.g. anisoles, anilines, etc.) has not yet been determined. Currently, the primary advantage of $\text{TpRu}(\text{II})$ systems is sufficient activity to enable catalytic turnover under relatively ambient conditions (i.e. low olefin concentrations and 90 °C). The flexibility of the Tp ligand and the option of replacing CO with other neutral, two-electron donating ligands offer the possibility of tuning future catalysts for improved properties.

In comparison with the $\text{Ru}(\text{II})$ systems, $\text{Ir}(\text{III})$ catalysts have more tolerance of olefin functionality. For example, hydroarylation of styrenes, acrylates, and dialkyl olefins is possible, although the number of turnovers is significantly reduced compared with the hydroarylation of ethylene using $\text{Ir}(\text{III})$ catalysts. The compatibility of the $\text{Ir}(\text{III})$ systems with heteroaromatic substrates has not been reported; hydroarylation of ethylene with chlorobenzene is possible, however, and gives *m*-, *p*- and *o*-chloroethylbenzene in 10.5:5.2:1 ratio. Chlorobenzene reacts more slowly than toluene or ethylbenzene indicating that electron-withdrawing groups deactivate the arene toward the metal-mediated C–H activation step. Consistent with this result, attempted hydroarylation of ethylene using pentafluorobenzene and $[\text{Ir}(\mu\text{-acac-O},\text{O},\text{C}^3)(\text{acac-O},\text{O})(\text{acac-C}^3))_2]$ as catalyst results in no observed reaction.

Important questions for this class of catalyst include whether more active systems can be accessed and if increased selectivity/functional group tolerance can be achieved. Given the importance of C–C bond-forming reactions that involve metal-mediated C–X (X = halide or trifluoromethanesulfonate) activation of an aromatic substrate [10–14], the development of catalysts that mediate selective C–C bond formation of aromatic compounds based on C–H activation would complement current methods and be a valuable addition to the toolbox of synthetic organic chemists. The possibility of increasing catalyst activity has been addressed using computational studies [15]. The seminal result from this study is the conclusion that electron density at the metal center has an inverse effect on the rates of C–H activation and olefin insertion. Thus, it has been predicted that as the activation barrier for C–H activation is reduced, the activation barrier for olefin insertion will increase, thereby placing an upper limit on catalyst activity; it has, however, been suggested that alteration of the σ -framework could lead to more efficient catalysts.

Experimental

Preparation of $\text{TpRu}(\text{CO})(\text{NCMe})(\text{Ph})$

$\text{TpRu}(\text{CO})_2(\text{Me})$ [1] (0.5239 g, 1.36 mmol) and Me_3NO (0.2040 g, 2.72 mmol) were heated under reflux in approximately 25 mL acetonitrile for 40 min. The solution was cooled to room temperature, neutral alumina (5 g) was added, and the volatiles were removed under reduced pressure. The green–yellow crude reaction mixture was flashed on a plug of neutral alumina using dichloromethane (~200 mL). Volatiles were removed from the eluent and the resulting solid was washed with hexanes to give a white solid. The solid, $\text{TpRu}(\text{CO})(\text{NCMe})(\text{Me})$, was collected and dried under vacuum (0.3601 g, 67 % yield). $\text{TpRu}(\text{CO})(\text{NCMe})(\text{Me})$ (0.538 g, 1.35 mmol) was dissolved in a mixture of benzene (16 mL) and acetonitrile (7 mL, 0.135 mol) and the solution was heated in a screwcap pressure tube to 90 °C for approximately 40 h. The volatiles were removed in vacuo, and the remaining solid was dissolved in a small amount of dichloromethane followed by precipitation with pentane. Collection of the resulting solid yielded a white powder in 68 % yield that was pure by NMR spectroscopy. To obtain product pure by elemental analysis, the resulting solid was purified by flash chromatography through a plug of neutral alumina using dichloromethane as eluent. The product was collected and the solvent volume was reduced to approximately 10 mL under reduced pressure. Precipitation with pentane yielded the pure product as a white solid.

Hydrophenylation of Ethylene Using $\text{TpRu}(\text{CO})(\text{NCMe})(\text{Ph})$

A representative catalytic reaction is described. $\text{TpRu}(\text{CO})(\text{NCMe})(\text{Ph})$ (0.021 g, 0.046 mmol) was dissolved in 4.1 mL (0.0456 mol) distilled benzene and decane (0.269 mL, 1.38 mmol) was added to the homogeneous solution as internal standard. The solution was placed in a thick-walled glass reaction vessel and charged with 25 psig ethylene. The tube was then placed in an oil bath heated to 90 °C. Periodically the tube was removed from the oil bath and plunged into an ice bath. A sample (0.1 mL) of the reaction solution was removed under a purge of dinitrogen and the tube was quickly returned to the oil bath and ethylene pressure was restored. The removed samples (~1 μL) were analyzed by GC–FID.

Preparation of $\text{Ir}(\text{O},\text{O-acac})_2(\text{C-acac})(\text{H}_2\text{O})$

$\text{IrCl}_3(\text{H}_2\text{O})_x$ (54.11 % Ir, 1 g, 2.82 mmol), 2,5-pentadione (10 mL, 9.75 mmol), and NaHCO_3 (1 g, 11.9 mmol) were added to a round-bottomed flask equipped with a reflux condenser vented to an oil bubbler. The mixture was heated to gentle reflux with stirring for 48 h. During this time a yellow solid precipitated. The reaction mixture was cooled to room temperature and the solid was collected as crude product. The yellow solid was dissolved in 200 mL H_2O at room temperature with vigorous stirring and the solution was filtered and concentrated under vacuum to give 650 mg (45 %) $\text{Ir}(\text{O},\text{O-acac})_2(\text{C-acac})(\text{H}_2\text{O})$ as a yellow microcrystalline solid.

Hydrophenylation of Propene Using Ir(III)

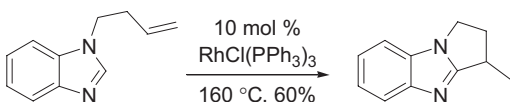
A 3-mL stainless steel autoclave equipped with a glass insert and a magnetic stir bar was charged with 1 mL distilled benzene and 3–5 mg (5 mmol, ~0.1 mol%) catalyst. The reactor was degassed with nitrogen and pressurized with 0.96 MPa propylene and 2.96 MPa nitrogen. The autoclave was heated for 30 min in a well stirred heating bath maintained at 180 °C. The liquid phase was sampled and product yield was determined by GC–MS using methyl cyclohexane, introduced into the reaction solution after the reaction, as internal standard.

1.3.2.4 Catalytic Functionalization of N-Heterocycles via their Rhodium–Carbene Complexes

Sean H. Wiedemann, Jonathan A. Ellman, and Robert G. Bergman

1.3.2.4.1 Introduction and Fundamental Examples

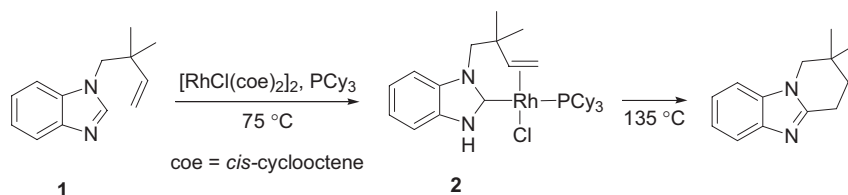
The *o*-functionalization of arenes directed by an embedded nitrogen atom ranks among the first examples of a directed catalytic C–H transformation [1]. Moore et al. demonstrated that pyridine can be *o*-acylated by CO and an olefin using $\text{Ru}_3(\text{CO})_{12}$ as catalyst [2]. Later, imidazoles, among other N-heterocycles, were also found to be active substrates for this reaction [3]. Other than early Zr-catalyzed studies [1], however, at the beginning of this work we were unable to uncover any examples of C-alkylation of N-heterocycles by olefins. The $\text{RhCl}(\text{PPh}_3)_3$ -catalyzed cyclization of olefin tethered benzimidazoles was our first effort in this area (Scheme 1) [4]. In prior work, Wilkinson's catalyst had proven effective for C–H transformations involving a *pendant* directing group [5]. Despite this precedent, mechanistic evidence suggests that a unique mechanism is operative in our reaction.



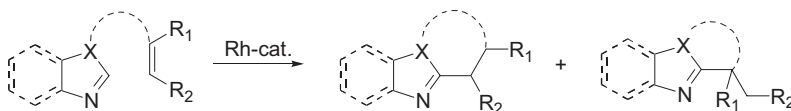
Scheme 1. Initial cyclization result.

When benzimidazole **1** was treated with a stoichiometric amount of an optimized Rh-catalyst mixture ($[\text{RhCl}(\text{coe})_2]_2$ and PCy_3), a single catalyst–substrate complex (**2**) was isolated (Scheme 2) [6]. Structural studies of **2** revealed an unusual ligand binding mode in which the organic fragment is bound to rhodium as an N-heterocyclic carbene (NHC). Kinetic studies showed our catalytic cycle to be the first known example involving a reactive M–NHC intermediate. This new-found mechanistic understanding illuminates general structural requirements for Rh–NHC-mediated arene addition (Scheme 3). These specifications parallel those for the formation of stable NHCs having two donating heteroatoms flanking an sp^2 -hybridized carbon [7].

This chapter covers the intramolecular cyclization of olefin-tethered benzimidazoles and the intermolecular C–H addition of azoles to olefins [8]. These reactions



Scheme 2. Discovery of catalyst resting state.



Scheme 3. General reaction.

can be conducted using a catalyst mixture of commercially available materials at neutral pH. Mild Lewis acids or, more conveniently, Brønsted acids have been shown to promote the desired reaction. Microwave heating can also significantly reduce reaction times [9].

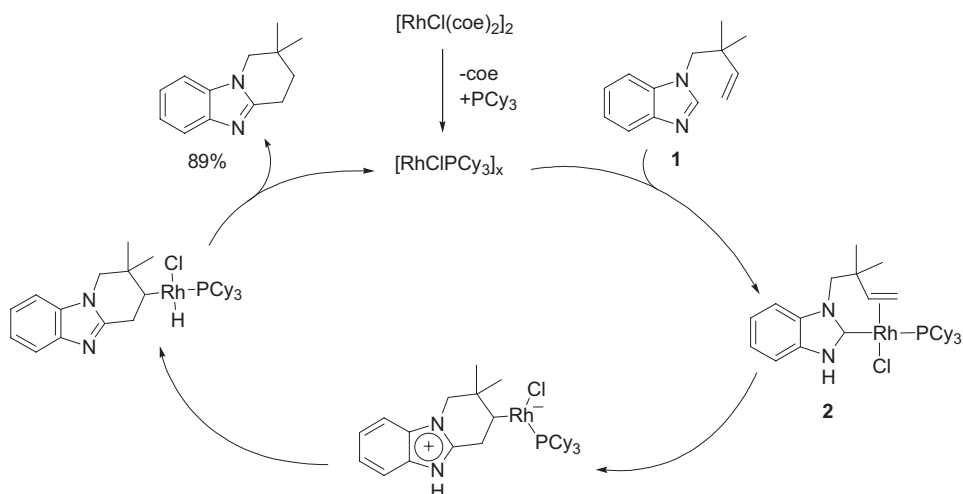
Some variants of our central reaction have been discovered. Consistent with the notion that NHC ligands are stable in the absence of aromatic π -stabilization, a non-aromatic N-heterocycle, 4,4-dimethyl-2-oxazoline (**3**), can be added to olefins in the presence of a rhodium catalyst [10]. The optimized reaction conditions are especially mild, making this an effective method for preparation of protected carboxylic acids.

Close inspection of **2** reveals that it can be thought of as a metal–aryl complex in a low oxidation state. Thus it meets the conditions for another type of C–H transformation – cross-coupling. Various N-heterocycles bearing the N-CH-X motif will react with aryl iodides, under the action of rhodium catalysis, to give arylated products in moderate yield [11].

1.3.2.4.2 Mechanism

The proposed catalytic cycle for the annulation of **1** has been chosen as a representative example of the C–H transformations discussed in this chapter (Scheme 4). Formation of the isolable catalyst resting state **2** occurs at a temperature well below that required for catalytic activity, suggesting that the initial C–H activation steps are rapid [6]. The formation of **2** from **1** and Rh/PCy_3 probably begins with coordination of a nitrogen lone-pair to Rh(I) [12]. Studies are in progress to define a specific microscopic pathway in the subsequent tautomerization/coordination to give **2**, but C–H to N–H tautomerization is certainly crucial to catalyst activity because all suitable substrates feature an unsaturated nitrogen atom adjacent to the site of coupling.

DFT calculations performed on a simplified version of **2** indicate that the transition state for carbometallation of the pendant olefin is the highest energy barrier of the overall reaction [13]. Subsequent rapid steps, including proton-transfer and



Scheme 4. Representative mechanism of olefin arylation.

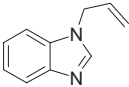
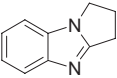
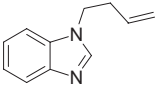
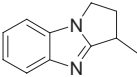
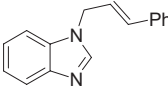
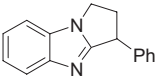
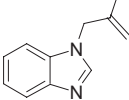
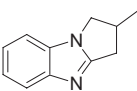
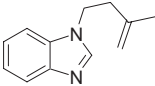
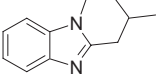
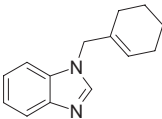
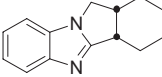
reductive elimination, are needed to liberate unsaturated Rh, which is rapidly reconverted to resting-state 2.

This Rh(I)-based mechanism does not properly explain the pronounced rate acceleration observed on addition of HCl. Rather, we suggest that the well-known propensity of Rh(I) to oxidatively add HCl evokes a different, Rh(III)-based mechanism. The elementary steps along such a pathway (β -hydride insertion then C–C reductive elimination) differ substantially from those depicted in Scheme 4. Despite this uncertainty, our current mechanistic understanding of the non- H^+ mediated reaction constitutes a satisfactory model because it has led to the successful refinement and expansion of our initial findings.

1.3.2.4.3 Scope and Limitations

The intramolecular coupling of benzimidazoles using a Rh(I)/ PCy_3 catalyst is quite general with respect to substitution on the pendant olefin (Table 1, Column A) [4]. Alkenes bearing up to three substituents can be cyclized successfully. When cyclization to different ring sizes is possible, the reaction tends to be selective for formation of five-membered rings (Table 1, Entry 2), although steric factors can override this preference (Table 1, Entry 5). The best yields and selectivity are obtained when competing Rh-catalyzed positional isomerization of the pendant olefin is slow or impossible.

Table 1. Substrate generality of intramolecular coupling.

Entry	Substrate	Product	Yield (%)			
			Column Heating:	A conventional	B microwave	C
			Catalyst:	Rh/PCy ₃ ^a	Rh/PCy ₃ ·HCl ^b	RhCl(PPh ₃) ₃ ^c
1				70 ^d	50 ^d	59 ^d
2				79	76	55
3				–	62	42
4				82	97	64
5				71 ^d	78	59
6				75 ^d	–	–

^a Conditions: 5 mol % $\frac{1}{2}$ [RhCl(coe)₂]₂, 7.5 mol % PCy₃, THF or toluene, 160–180 °C, 1–3 d. [4]

^b Conditions: 5 mol % $\frac{1}{2}$ [RhCl(coe)₂]₂, 5 mol % PCy₃, o-dichlorobenzene/acetone, 225–250 °C, 6–12 min. [9]

^c Conditions: 10 mol % RhCl(PPh₃)₃, 250 °C, 20 min. [9]

^d Reactions run with 2x the normal catalyst loading.

The greatest limitations of our initial method in respect to, for example, industrial applications, are the air-sensitive nature of the catalyst and the high temperatures and long reaction times required. Two revised methods utilizing microwave heating have been developed to overcome these difficulties [9]. Microwave heating as a strategy for increasing reaction rate and yield has become well-accepted in both academic and industrial laboratories for a variety of chemical transformations [14].

The first revised method (Table 1, Column B) offers reduced air sensitivity and takes advantage of beneficial Brønsted acid additive effects by making use of PCy₃

protected as its HCl salt. The combined benefits of the acid additive and microwave heating lead to yields after 12 min of heating that generally exceed those obtained from 20 h of conventional heating without additives.

The second revised method (Table 1, Column C) offers the most operationally simple reaction conditions. Commercially available, air-stable Wilkinson's catalyst is used instead of a Rh/phosphine mixture, and the reactions are complete in less than 20 min. Isolated yields continue to be in the useful range without the need for special air-sensitive techniques.

The additive-modified catalyst mixture developed for intramolecular olefin coupling is sufficiently active to catalyze the analogous intermolecular reaction. A variety of five-membered N-heterocycles can be catalytically alkylated at the C-2 position (Table 2) [8]. Additional functional groups on the heterocycle [15] (Table 2, Entry 1) and on the olefin (Table 3) are well tolerated. Products corresponding to linear addition are usually obtained exclusively, even when the olefin is rapidly isomerized under the reaction conditions.

Table 2. Heterocycle generality of intermolecular coupling.^a

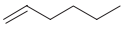
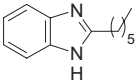
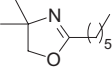

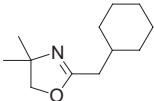

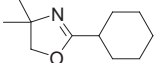
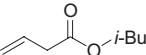
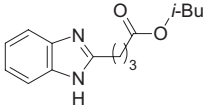
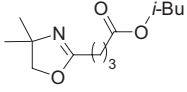
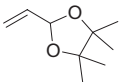
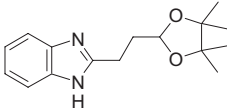
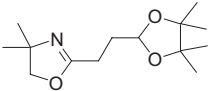
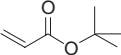
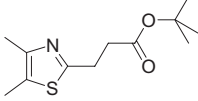
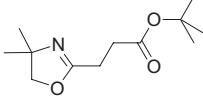
Entry	Heterocycle	Product	Substitution	Yield (%)
1			R = H R = OMe R = COOMe R = Cl	96 94 ^b 89 ^b 93 ^b
2			X = NMe X = S X = O	67 97 77
3			—	99
4			—	86 ^c

^a Conditions: 5 mol % $\frac{1}{2}$ [RhCl(coe)₂]₂, 7.5 mol % PCy₃, 5 mol % 2,6-lutidine·HCl, 5 equiv 3,3-dimethylbutene, THF, 150 °C. [8]

^b Conditions: 5 mol % $\frac{1}{2}$ [RhCl(coe)₂]₂, 5 mol % PCy₃·HCl, 5 equiv 3,3-dimethylbutene, THF, 150 °C. [10]

^c Conditions: 5 mol % $\frac{1}{2}$ [RhCl(coe)₂]₂, 5 mol % PCy₃·HCl, 2.5 mol % PCy₃, 5 equiv 3,3-dimethylbutene, THF, 45 °C. [10]

Table 3. Alkene generality of intermolecular coupling of azoles and 3.

Entry	Alkene	Azole product ^a	Yield (%)	Azoline product ^b	Yield (%)
1			80		74
2		–	–		79
3		–	–		57
4			87 ^c		71 ^d
5			60 ^c		58 ^d
6			93 ^c		59 ^d

^a Conditions: 1 equiv benzimidazole or 4,5-dimethylthiazole, 5 mol % $\frac{1}{2}$ [RhCl(coe)₂]₂, 7.5 mol % PCy₃, 5 mol % 2,6-lutidine·HCl, 5 equiv alkene, THF, 150 °C. [8]

^b Conditions: 1 equiv 4,4-dimethyl-2-oxazoline (3), 5 mol % $\frac{1}{2}$ [RhCl(coe)₂]₂, 5 mol % PCy₃·HCl, 2.5 mol % PCy₃, 5 equiv alkene, THF, 45 °C. [10]

^c Reactions run with 2x the normal catalyst loading.


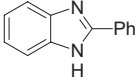

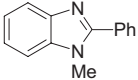

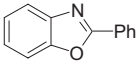
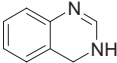
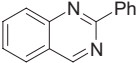

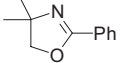
^d Reactions run at 105 °C.

Olefins react with 4,4-dimethyl-2-oxazoline (3) much more efficiently (Table 3, azoline column) than they do with other (aromatic) substrates [10]. Rather than requiring reaction temperatures of 135–180 °C for the reaction to occur, addition of 3 to olefins is optimally conducted between 45 and 105 °C. The substrate scope of this reaction includes, for the first time, disubstituted alkenes (Table 3, azoline column, Entries 2 and 3). The coupling products of 3 with olefins can be deprotected to reveal carboxylic acids or elaborated further using well-known methods [16].

A variety of N-heterocycles can be catalytically phenylated with iodobenzene (Table 4) [11]. This reaction provides substrate scope complementary to that of existing Pd-catalyzed N-heterocycle arylation methods [17]. Both aromatic and non-aromatic heterocycles serve as suitable substrates. Dihydroquinazoline (Table 4,

Entry 4), in addition to being active toward arylation, is a good substrate for addition to alkenes [18].

Table 4. Heterocycle arylation with iodobenzene.^a

Entry	Heterocycle	Product	Temp. (°C)	Yield (%)
1			150	56
2			135	51
3			135	79
4			150	78
5			105	51

^a Conditions: 10 mol % $\frac{1}{2}$ [RhCl(coe)₂]₂, 40 mol % PCy₃, 4 equiv Et₃N, 2 equiv iodobenzene, THF, 150 °C. [11]

Experimental

2,3-Dihydro-2-methyl-1H-pyrrolo[1,2-a]benzimidazole (Table 1, Column C, Entry 4)

To a 2–5 mL process vial was added 103 mg (0.60 mmol) 1-(2-methylallyl)-1H-benzimidazole and 56 mg (0.060 mmol) RhCl(PPh₃)₃. The reaction vessel was flushed with N₂ for 1 min and then capped with a septum. A 3:1 *o*-dichlorobenzene–acetone mixture (3 mL, untreated) was added via syringe and the vial was placed in a Smith Synthesizer cavity and subjected to microwave radiation (300 W, normal absorption) with stirring. A pre-set temperature of 250 °C was reached rapidly (<1 min) and sustained for 20 min. On cooling with 40 psig compressed air the vessel was uncapped and the contents evaporated to dryness in a Savant evaporator. The residue was then taken up in ethyl acetate (20 mL) and washed with 1 M HCl (3 × 20 mL). The acidic layers were combined and washed with ethyl acetate, and then made alkaline to pH 9 by slow addition of solid K₂CO₃. The resulting basic solution was then extracted with CH₂Cl₂ (3 × 20 mL). The organic layers were combined, dried over MgSO₄, filtered, and evaporated to dryness; TLC (silica, hexanes–ethyl acetate, 1:1, with 1 % Et₃N): R_F = 0.20. The fraction with R_F = 0.20 was isolated by flash chromatography: 66 mg (64 %) as a pale orange solid with m.p. 88 °C. ¹H NMR (CDCl₃, 500 MHz) δ = 7.70–7.68 (m, 1H, Ar-H), 7.27–7.17 (m, 3H,

Ar-H), 4.23 (dd, 1H, $J=10$, 7.5 Hz, 1-H), 3.63 (dd, 1H, $J=10$, 6 Hz, 1-H), 3.25–3.13 (m, 2H, 2,3-H), 2.67 (dd, 1H, $J=16$, 6, 3-H), 1.32 (d, 3H, $J=6.5$ Hz, 3-CH₃).

2-Hexyl-4,4-dimethyl-2-oxazoline (Table 3, Azoline column, Entry 1)

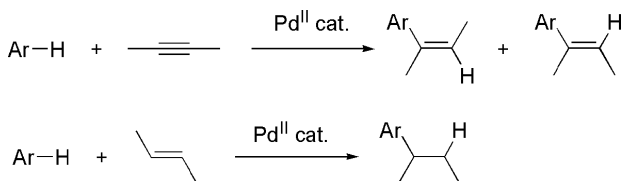
In a nitrogen atmosphere glove-box, a glass-walled vessel equipped with a stop-cock (20 mL) was filled with a solution of 1-hexene (420 mg, 5.0 mmol), [RhCl(coe)₂]₂ (18.0 mg, 0.050 mmol relative to monomer), PCy₃·HCl (16.0 mg, 0.050 mmol) [19], and PCy₃ (7.0 mg, 0.025 mmol) in THF (6.7 mL). Immediately before closing the Kontes seal, 99.1 mg (1.0 mmol) 4,4-dimethyl-2-oxazoline (**3**) was added. The reaction mixture was heated at 45 °C for 18 h and then cooled to 25 °C. The reactor was opened in air and excess acid was neutralized by addition of Et₃N (0.5 mL); TLC (silica, pentane–diethyl ether, 1:1, I₂ stain): $R_F=0.3$. The reaction suspension was mixed with silica, concentrated to dryness using a rotary evaporator, and the fraction with $R_F=0.3$ was isolated by flash chromatography: 136 mg (74 %) as colorless oil. IR: 1668 cm⁻¹ (C=N). ¹H NMR (CDCl₃, 500 MHz): $\delta=3.88$ (s, 2H, 3-H), 2.22 (t, 2H, $J=7.8$ Hz, 1'-H), 1.60 (m, 2H, 2'-H), 1.4–1.2 (m, 6H, 3'-5'-H), 1.21 (s, 6H, 4-CH₃), 0.86 (t, 3H, $J=6.8$ Hz, 6'-H).

1.3.2.5 Fujiwara Reaction: Palladium-catalyzed Hydroarylations of Alkynes and Alkenes

Yuzo Fujiwara and Tsugio Kitamura

1.3.2.5.1 Introduction and Fundamental Examples

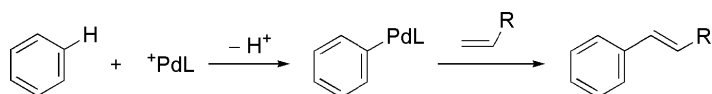
The catalytic activation of aromatic C–H bonds leading to useful addition with new C–C bond formation is of considerable interest in organic synthesis and industrial processes, because it would provide simple and economical methods for producing aryl-substituted compounds directly from simple arenes, as shown in Scheme 1.



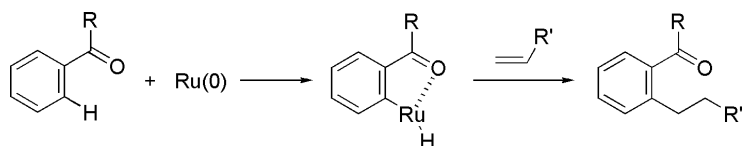
Scheme 1. General equations for hydroarylation of alkynes or alkenes.

Study of the reactivity of aromatic C–H bonds in the presence of transition metal compounds began in the 1960s despite the quite early discovery of Friedel–Crafts alkylation and acylation reactions with Lewis acid catalysts. In 1967, we reported Pd(II)-mediated coupling of arenes with olefins in acetic acid under reflux[1]. The reaction involves the electrophilic substitution of aromatic C–H bonds by a Pd(II) species, as shown in Scheme 2, and this is one of the earliest examples of aromatic C–H bond activation by transition metal compounds. Al-

though the direct use of aromatic compounds in synthesis is generally restricted to activated groups (e.g. C–Br, C–Cl bonds) other than the C–H bonds, manufacture of aryl halides generally is not an environmentally friendly process and thus the future of bulk synthesis of aromatic compounds may lie in the direct transformation of C–H bonds. Activation of aromatic C–H bonds by ortho-chelating-assisted oxidative addition to low-valent transition metal compounds (Scheme 3), leading to addition to C–C multiple bonds, has been recognized as another promising route (see Chapter III.1.3.2.1) [2].

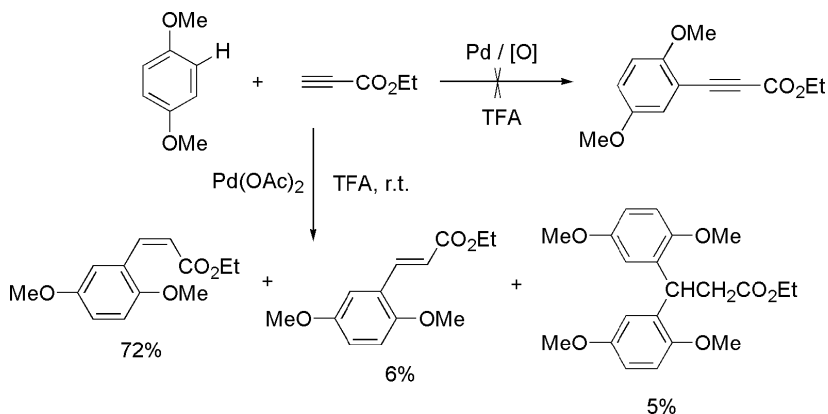


Scheme 2. C–H Bond transformation by electrophilic substitution.



Scheme 3. C–H bond transformation by ortho-chelating assistance (see Chapter III.1.3.2.1).

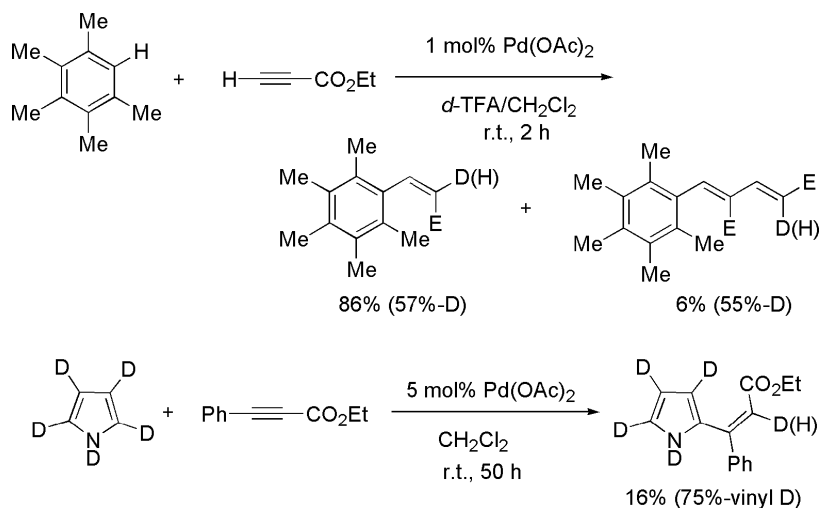
In our attempt to extend the coupling reaction of arenes with alkenes to the coupling with alkynes, as shown in Scheme 4, it was found that the reaction of arenes with ethyl propiolate in TFA (trifluoroacetic acid) gave addition products instead of a coupling product [3]. This addition reaction has been extended to various alkynes and various arenes and also to intramolecular reactions for synthesis of heterocycles such as coumarins, quinolines, and thiocoumarins.



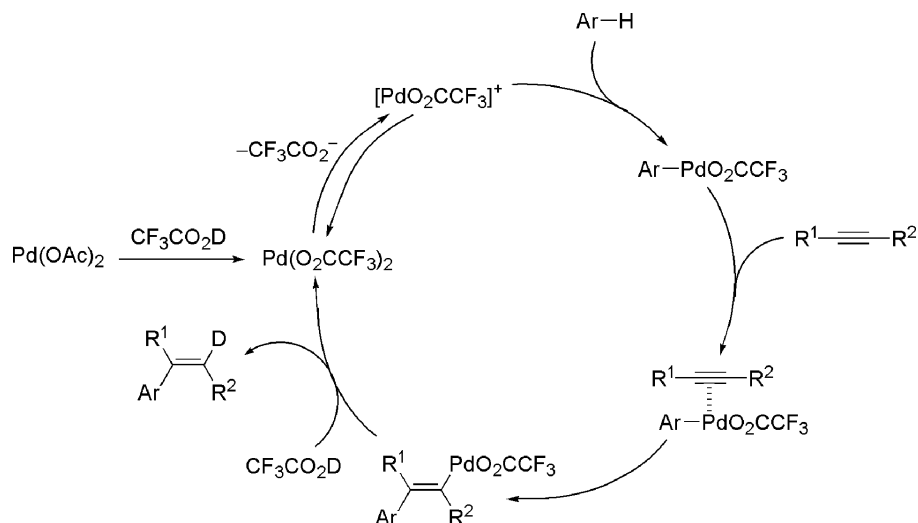
Scheme 4. Reactions of arenes with alkynes in the presence of a Pd catalyst.

1.3.2.5.2 Mechanism

Isotope experiments revealed that D-atoms were incorporated to the vinyl position of adducts either in inter- or intramolecular reactions in *d*-TFA (Scheme 5) [3b, c]. Reaction of heteroarenes with alkynoates in AcOD gave similar results [4]. Also, addition of heteroaromatic C–D bonds to the C–C multiple bonds and the large isotope effect ($k_{\text{H}}/k_{\text{D}} = 3$) between pyrrole and *d*₅-pyrrole in the reaction with ethyl phenylpropiolate were observed.



Scheme 5. Isotope experiments for hydroarylations of alkynes.



Scheme 6. Possible mechanism for Pd-catalyzed hydroarylation of alkynes.

Thus, a possible mechanism involving σ -aryl-Pd complexes similar to those involved in the coupling reaction of arenes with olefins has been suggested. Scheme 6 shows the possible mechanism of the hydroarylations. The facile formation of similar aryl-Pd complexes from Pd(II) and arenes in TFA has been indicated by the coupling of arenes with arenes, and also demonstrated by formation of aromatic acids from simple arenes with carbon monoxide [5]. The formation of vinyl-Pd complexes has been suggested by the formation of adducts of two alkynes and one arene. Use of TFA as solvent facilitates the generation of a highly cationic $[\text{Pd(II)O}_2\text{CCF}_3]^+$ species to form σ -aryl-Pd complexes by electrophilic substitution of aromatic C-H bonds.

It is considered that the hydroarylation of alkenes proceeds with a mechanism similar to that depicted in Scheme 6.

1.3.2.5.3 Scope and Limitations

Table 1 shows that a variety of commercially available aromatic compounds undergo Pd-catalyzed hydroarylations. Generally electron-rich aromatics give good results [3], consistent with a mechanism involving electrophilic aromatic C-H bond activation. This type of hydroarylation has high chemoselectivity with Br and OH substituents on aromatic compounds. Besides ethyl propiolate, terminal and internal alkynes including substituted propiolates, arylalkynes, and 3-butyne-2-ones are used for this hydroarylation. In addition to Pd(OAc)_2 , a Pt(II) catalyst, $\text{PtCl}_2/2\text{AgOAc/TFA}$, has catalytic activity with a higher selectivity.

As shown in Table 2, reaction of heteroaromatic compounds with alkynoates occurs under very mild conditions [4, 6]. Heteroaromatic compounds such as pyrroles, furans, and indoles readily hydroarylate alkynoates at room temperature in the presence of a catalytic amount of Pd(OAc)_2 in acetic acid or CH_2Cl_2 , usually affording *cis*-heteroarylalkenes. This reaction provides a synthetic route to heteroarylalkenes, especially *cis*-alkenes, from simple heteroaromatic compounds.

The intermolecular reaction of phenols with propiolates in TFA in the presence of a catalytic amount of Pd(OAc)_2 affords coumarin derivatives [3c, 7]. The results are summarized in Table 3. The coumarins are obtained in high yields from electron-rich phenols such as 3,4,5-trimethoxyphenol, 3,5-dimethoxyphenol, 3-methoxyphenol, 2-naphthol, and 3,4-methylenedioxyphenol. Various alkynoates, including diethyl acetylenedicarboxylate, give the corresponding coumarins in good-to-high yields.

The intramolecular version of this reaction provides a general method for synthesis of biologically active heterocycles, for example coumarins, quinolinones, and thiocoumarins, as shown in Schemes 7 and 8 [3a, c]. The reaction tolerates a variety of functional groups, for example Br, CHO, etc.

Very recently, it was found that montmorillonite-enwrapped Pd(II) catalyst had high activity in hydroarylations of alkynes or alkenes [8]. The results are summarized in Table 4. The catalyst could be reused without any loss of activity.

Table 1. Representative examples of the hydroarylation of alkynes.

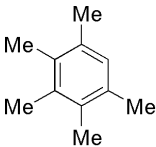
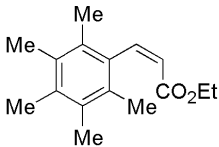
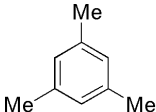
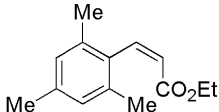
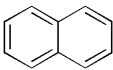
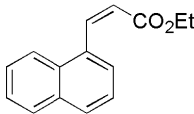
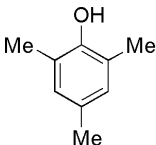
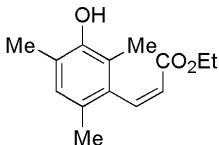
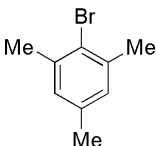
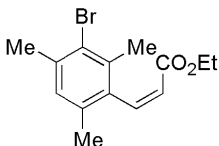
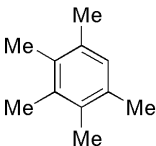
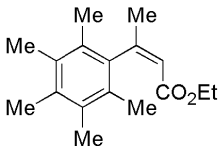
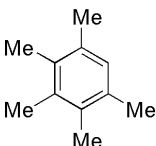
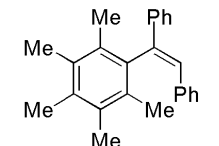
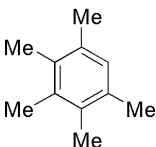
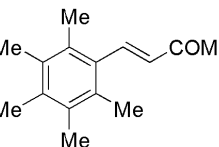
Arenes	Alkynes	Products	Yield (%)
	$\equiv\text{CO}_2\text{Et}$		85
	$\equiv\text{CO}_2\text{Et}$		49
	$\equiv\text{CO}_2\text{Et}$		45
	$\equiv\text{CO}_2\text{Et}$		57
	$\equiv\text{CO}_2\text{Et}$		46
	$\text{Me}-\equiv-\text{CO}_2\text{Et}$		78
	$\text{Ph}-\equiv-\text{Ph}$		58
	$\equiv\text{COMe}$		92

Table 2. Representative examples of hydroarylation of alkynoates by heteroaromatic compounds.


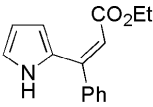

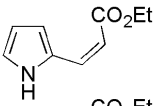

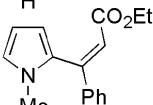
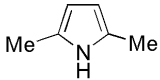
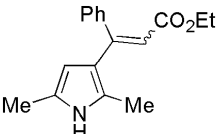
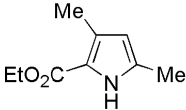
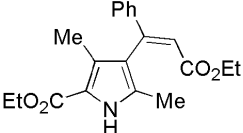
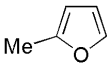
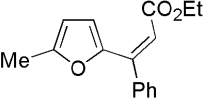
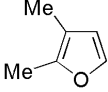
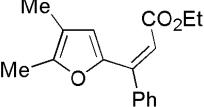
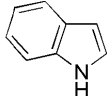
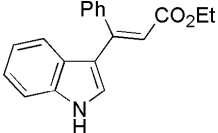
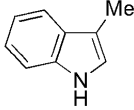
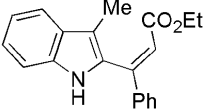
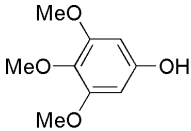
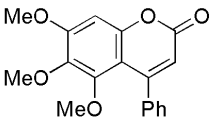
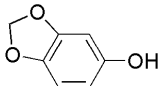
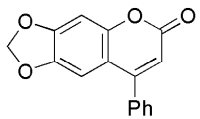
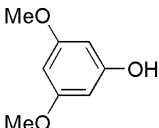
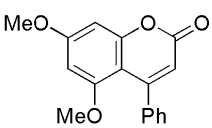
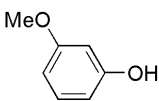
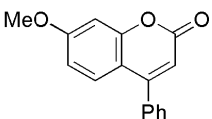
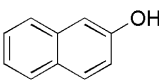
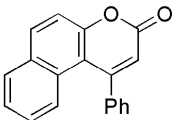
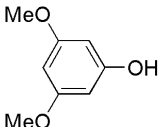
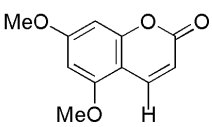
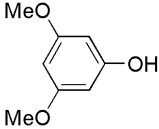
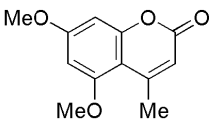
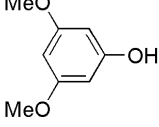
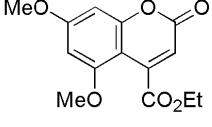
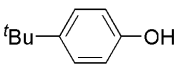
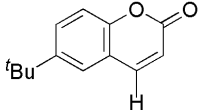
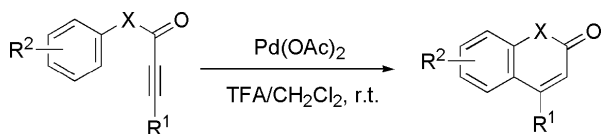
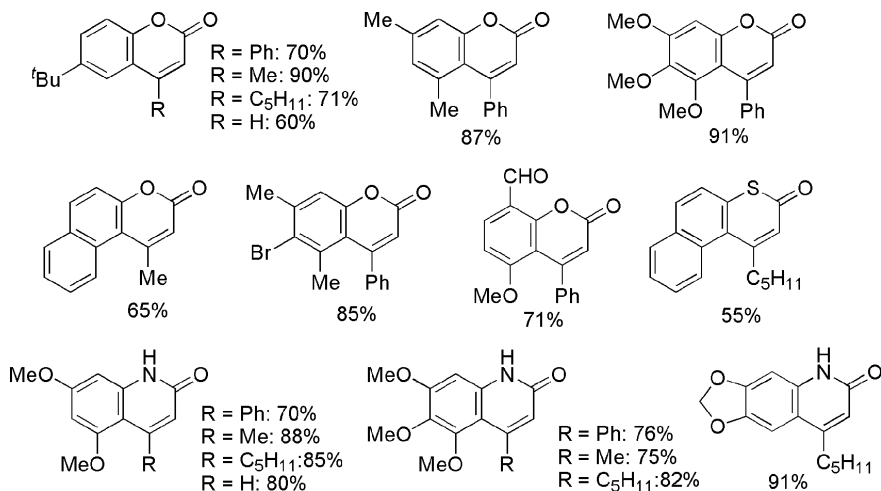
Heteroaromatics	Alkynoates	Products	Yield (%)
	$\text{Ph}-\text{C}\equiv\text{C}-\text{CO}_2\text{Et}$		78
	$\text{C}\equiv\text{C}-\text{CO}_2\text{Et}$		52
	$\text{Ph}-\text{C}\equiv\text{C}-\text{CO}_2\text{Et}$		83
	$\text{Ph}-\text{C}\equiv\text{C}-\text{CO}_2\text{Et}$		71 (E/Z = 2/1)
	$\text{Ph}-\text{C}\equiv\text{C}-\text{CO}_2\text{Et}$		66
	$\text{Ph}-\text{C}\equiv\text{C}-\text{CO}_2\text{Et}$		72
	$\text{Ph}-\text{C}\equiv\text{C}-\text{CO}_2\text{Et}$		66
	$\text{Ph}-\text{C}\equiv\text{C}-\text{CO}_2\text{Et}$		78
	$\text{Ph}-\text{C}\equiv\text{C}-\text{CO}_2\text{Et}$		69

Table 3. Pd(II)-catalyzed reaction of phenols with alkynoates.

Phenols	Alkynoates	Products	Yield (%)
	$\text{Ph}-\text{C}\equiv\text{C}-\text{CO}_2\text{Et}$		87
	$\text{Ph}-\text{C}\equiv\text{C}-\text{CO}_2\text{Et}$		93
	$\text{Ph}-\text{C}\equiv\text{C}-\text{CO}_2\text{Et}$		56
	$\text{Ph}-\text{C}\equiv\text{C}-\text{CO}_2\text{Et}$		85
	$\text{Ph}-\text{C}\equiv\text{C}-\text{CO}_2\text{Et}$		88
	$\text{H}-\text{C}\equiv\text{C}-\text{CO}_2\text{Et}$		59
	$\text{Me}-\text{C}\equiv\text{C}-\text{CO}_2\text{Et}$		97
	$\text{EtO}_2\text{C}-\text{C}\equiv\text{C}-\text{CO}_2\text{Et}$		47
	$\text{H}-\text{C}\equiv\text{C}-\text{CO}_2\text{Et}$		51

**Scheme 7.** Intramolecular hydroarylation of alkynes.**Scheme 8.** Typical heterocycles from intramolecular hydroarylation.**Table 4.** Pd(II)-Montmorillonite-catalyzed hydroarylation of alkynes or alkenes.

Aromatics	Alkynes or alkenes	Products	Yield (%)
	Ph—C≡C—CO ₂ Et		83
	Ph—C≡C—Ph		78
	An—CH=CH—CO ₂ H		100
	An—CH=CH—CO ₂ C ₈ H ₁₇		78

Experimental

Hydroarylation of Ethyl Propiolate by Pentamethylbenzene. Ethyl (2Z)-3-(pentamethylphenyl)propenoate

Ethyl propiolate (0.475 g, 4.9 mmol) was added, with stirring, to a cold mixture of pentamethylbenzene (1.51 g, 10.2 mmol), Pd(OAc)₂ (10 mg, 0.045 mmol), TFA (4 mL), and CH₂Cl₂ (1 mL) on an ice–water bath and the mixture was stirred for 5 min. The mixture was then warmed to room temperature and stirred for 3 h. The reaction mixture was poured into saturated NaCl solution and extracted with ether. The extract was washed with saturated NaCl, neutralized with Na₂CO₃ solution, dried over anhydrous Na₂SO₄, and the solvent was evaporated in vacuo. Two compounds were isolated by column chromatography on silica gel with 8:1 hexane–AcOEt as eluent to give ethyl (2Z)-3-(pentamethylphenyl)propenoate, 1.05 g (88%), as white crystals, mp 71.8–72.3 °C: ¹H NMR (300 MHz, CDCl₃) δ 1.09 (t, *J* = 7.2 Hz, 3H, CH₃), 2.14 (s, 6H, 2CH₃), 2.19 (s, 6H, 2CH₃), 2.22 (s, 3H, CH₃), 4.01 (q, *J* = 7.2 Hz, 2H, OCH₂), 6.12 (d, *J* = 12.0 Hz, 1H, vinyl), 7.12 (d, *J* = 12.0 Hz, 1H, vinyl). ¹³C NMR (75 MHz, CDCl₃) δ 13.84, 16.22, 16.60, 17.46, 59.61, 122.01, 129.61, 131.72, 133.11, 133.79, 146.32, 165.23. IR (CHCl₃, cm^{−1}) 1724 (C=O). Ethyl (2E,4Z)-4-(ethoxycarbonyl)-5-(pentamethylphenyl)-2,4-pentadienoate, 0.05 g (6%), as colorless crystals with mp 60.8–62.0 °C: ¹H NMR (300 MHz, CDCl₃) δ 0.87 (t, *J* = 6.9 Hz, 3H, CH₃), 1.32 (t, *J* = 6.9 Hz, 3H, CH₃), 2.12 (s, 6H, 2CH₃), 2.18 (d, 6H, 2CH₃), 2.22 (s, 3H, CH₃), 3.97 (q, *J* = 6.9 Hz, 2H, OCH₂), 4.25 (q, *J* = 6.9 Hz, 2H, OCH₂), 6.17 (d, *J* = 15.9 Hz, 1H, vinyl), 7.25 (d, 1H, vinyl), 7.50 (d, *J* = 15.9 Hz, 1H, vinyl). ¹³C NMR (75 MHz, CDCl₃) δ 13.40, 14.26, 16.19, 16.67, 17.78, 60.47, 60.53, 120.41, 130.37, 132.04, 132.44, 133.98, 134.44, 141.48, 145.25, 166.01. IR (CHCl₃, cm^{−1}) 1734 (C=O), 1716 (C=O).

Pd(II)-catalyzed Reaction of 3,4,5-Trimethoxyphenol with Ethyl Phenylpropiolate. 5,6,7-Trimethoxy-4-phenylcoumarin

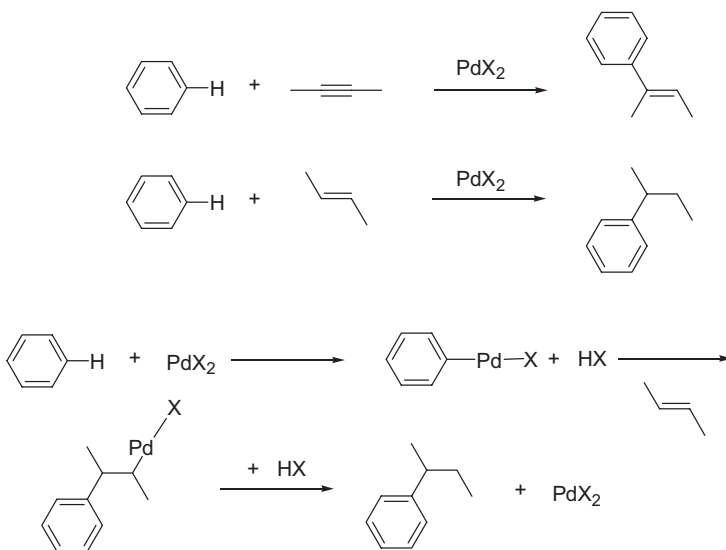
Ethyl phenylpropiolate (0.238 g, 2 mmol) was added to a cold mixture of Pd(OAc)₂ (5.6 mg, 0.025 mmol), 3,4,5-trimethoxyphenol (0.184 g, 1 mmol), and TFA (1.5 mL) on an ice–water bath. After stirring at the same temperature for 5 min, the mixture was stirred at room temperature for 6 h. The reaction mixture was then neutralized with aqueous NaHCO₃ solution, extracted with CH₂Cl₂, and the extract was dried over anhydrous Na₂SO₄ and concentrated. Flash column chromatography on silica gel with hexane–AcOEt as eluent gave 0.258 g (87%) 5,6,7-trimethoxy-4-phenylcoumarin as colorless crystals, mp 146.8–147.7 °C: ¹H NMR (300 MHz, CDCl₃) δ 3.26 (s, 3H, OCH₃), 3.79 (s, 3H, OCH₃), 3.94 (s, 3H, OCH₃), 6.07 (s, 1H, vinyl), 6.73 (s, 1H, ArH), 7.34 (m, 2H, Ph), 7.40 (m, 3H, Ph). ¹³C NMR (75 MHz, CDCl₃) δ 56.22, 60.88, 61.01, 96.23, 107.23, 114.02, 127.17, 127.46, 127.98, 138.98, 139.41, 151.04, 151.64, 155.35, 156.86, 160.58. IR (KBr, cm^{−1}) 1726 (C=O).

1.3.2.6 Palladium-catalyzed Oxidative Vinylation

Piet W. N. M. van Leeuwen and Johannes G. de Vries

1.3.2.6.1 Introduction

The reaction sequence in the vinylation of aromatic halides and vinyl halides, i.e. the Heck reaction, is oxidative addition of the alkyl halide to a zerovalent palladium complex, then insertion of an alkene and completed by β -hydride elimination and HX elimination. Initially though, C–H activation of a C–H alkene bond had also been taken into consideration. Although the Heck reaction reduces the formation of salt by-products by half compared with cross-coupling reactions, salts are still formed in stoichiometric amounts. Further reduction of salt production by a proper choice of aryl precursors has been reported (Chapter III.2.1) [1]. In these examples aromatic carboxylic anhydrides were used instead of halides and the co-produced acid can be recycled and one molecule of carbon monoxide is sacrificed. Catalytic activation of aromatic C–H bonds and subsequent insertion of alkenes leads to new C–C bond formation without production of halide salt by-products, as shown in Scheme 1. When the hydroarylation reaction is performed with alkynes one obtains arylalkenes, the products of the Heck reaction, which now are synthesized without the co-production of salts. No reoxidation of the metal is required, because palladium(II) is regenerated.



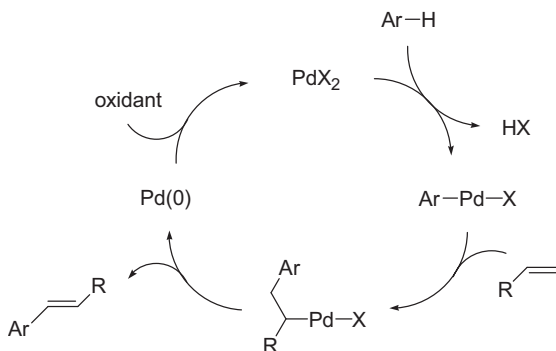
Scheme 1. Hydroarylation of alkenes and alkynes (see Chapter III.1.3.2.5).

The reactions shown in Scheme 1 require activation of the aromatic C–H bond by a metal and subsequent insertion of an alkene or alkyne in the aryl–carbon palladium bond (Chapter III.1.3.2.5). C–H activation has been the topic of many studies since the 1960s and several metal complex systems are known to induce

this reaction [2]. Here we will focus on activation by electrophilic metal systems based on palladium.

1.3.2.6.2 Palladium Catalyzed Oxidative Vinylation of Arenes

Initially, a stoichiometric reaction was observed. This involved arylation of alkenes giving alkenes, rather than alkanes as presented in Scheme 1. The sequence is shown in Scheme 2 in more detail. After insertion of the alkene β -H elimination occurs giving the arylalkene product and palladium(0). This reaction was first reported by Fujiwara in 1967 [3]. The catalytic version requires the re-oxidation of palladium(0) to palladium(II) by an oxidant [4a]. This oxidative, catalytic coupling of arenes and alkenes was published in 1969 by Fujiwara. Copper and silver acetate combined with dioxygen as the reoxidizing agents gave turnover numbers up to 5 for the formation of *trans*-stilbene from styrene and benzene [4a]. Turnover numbers up to 14 were achieved by Tsuji in 1984 by using *t*-butyl perbenzoate as the oxidant [4b]. Palladium benzoate is used as the catalyst, and acetic acid and benzene as the solvent; typically the reaction is performed at 100 °C. Similarly, furans were coupled with acrylates $\text{H}_2\text{C}=\text{CHCO}_2\text{R}$ ($\text{R} = \text{Me}, \text{Et}$) to give 3-(*E*)-furyl propenoates. In the absence of olefins, Pd-catalyzed benzoxylation of C_6H_6 , PhMe, and PhCl occurred to give the corresponding aryl benzoates. The regioselectivity showed that metalation was involved rather than a radical reaction. With the use of benzoquinone as stabilizing agent and *t*-BuOOH as the oxidant TON as high as 280 (90 °C, 15 h, AcOH solvent) have been reported [5]. Other oxidants such as H_2O_2 , MnO_2 , or AgO_2CPh were less effective.

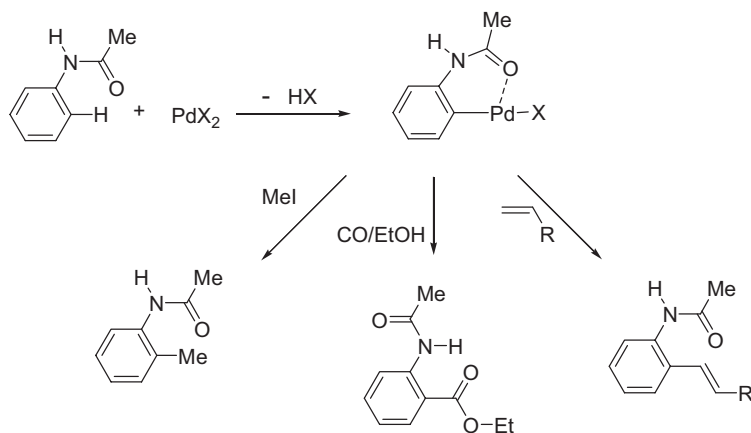


Scheme 2. Oxidative arylation of alkenes by electrophilic palladium(II).

1.3.2.6.3 ortho-Palladation Followed by Vinylation or Alkylation

Palladation of an arene is a very facile reaction when, before the C–H activation step, coordination of palladium to a nearby ligand functionality in the molecule occurs. The first report of a stoichiometric intramolecular palladation is probably the reaction of diazobenzene and palladium chloride by Cope in 1967 [6a]. Intramolecular palladation is a widespread reaction that has often been used as a starting point for synthesizing new molecules using insertion reactions in the arylpal-

ladium bond of unsaturated substrates [6b, c]. When the metal-to-ligand interaction is strong, as in imine and pyridine complexes, the reaction remains stoichiometric and catalysis is hard to achieve. Aromatic amides lead to weaker interactions between the amide ligand and palladium and under these conditions catalytic conversions have been reported. Orthovinylation of aromatic amides as a stoichiometric reaction was reported by Horino in 1981 [7]. The cyclopalladated intermediate has been isolated and characterized (Scheme 3).

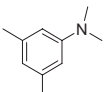
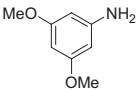
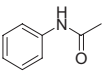


Scheme 3. Stoichiometric palladation and further reactions [7].

The highest yields for this reaction were obtained with an unsubstituted amide and with one containing a *p*-chloro substituent, with vinyl methyl ketone as the alkene. Use of styrene led to lower yields. The reaction of the intermediate acetanilidopalladacycle with methyl iodide, which produces *N*-*o*-tolylacetamide is interesting mechanistically [7b]. Stoichiometrically, full conversion was achieved, but attempts with catalysts gave only 10 turnovers and required the use of silver acetate to convert palladium iodide into the acetate, because palladium iodide does not have enough activity for metalation.

Catalytic results for the vinylation reaction were obtained by us by using rapid screening experiments with a parallel synthesis apparatus [8]. This setup enabled us to perform systematically a large number of experiments in a short time. From these experiments, in which catalyst, Ar-H, olefin, solvent, and oxidant were varied, a single lead emerged known already as the stoichiometric reaction reported above, the oxidative vinylation of acetanilides. Relevant results are summarized in Table 1. Aniline derivatives **1** and **2** are not reactive under the conditions tested (entries 1 and 2). In contrast, the reaction of acetanilide (**3**) with *n*-butyl acrylate proceeds smoothly and selectively at 80 °C using 2 mol% Pd(OAc)₂ and benzoquinone (BQ) as oxidant to yield *n*-butyl *E*-(2-acetamido)cinnamate **4** (Eq. 2) exclusively, albeit in moderate yield. No formation of the 3- or 4-substituted product was observed in any of the reactions performed, showing the importance of the ortho-directing and stabilizing effect of the amide group, as observed by Horino.

Table 1. Coupling of aniline derivatives with *n*-butyl acrylate using Pd(OAc)₂^a.

Entry	Substrate	Temp (°C)	Solvent	Additives	Yield (%)
1		1 80	HOAc	None	0
2		2 80	HOAc	None	0
3		80	HOAc	None	35
4		20	HOAc	None	54
5		20	HOAc/Toluene ^b	TsOH ^c	72
6		3 20	HOAc/NMP ^b	TsOH ^c	23
7		20	CF ₃ COOH	None	61
8		20	HOAc/Toluene ^b	NaCl ^c	0
9 ^d		20	HOAc/Toluene ^b	TsOH ^c	29

^a Substrate (3.0 mmol), *n*-butyl acrylate (3.3 mmol), Pd(OAc)₂ (0.06 mmol), BQ (3.0 mmol) in 6.75 mL of solvent. Yields are isolated yields

^b 2:1 ratio (v/v). NMP = *N*-methylpyrrolidinone

^c 1.5 mmol

^d Reaction performed using H₂O₂ as the oxidant

Remarkably, reducing the reaction temperature to 20 °C results in higher yields (Table 1, entries 3 and 4). Acetic acid is the solvent of choice and using mixtures (up to 1:1 v/v) of HOAc with CH₂Cl₂ or THF does not affect the yields to a large extent. No C–H activation of aromatic solvents, e.g. toluene, is observed under these conditions. Coordinating solvents, for example NMP, hamper the catalytic reaction (entry 6), because the solvent competes successfully for the coordination site with the substrate. The presence of a substoichiometric amount (0.5–1.0 equiv.) of *para*-toluenesulfonic acid (TsOH) has a large beneficial effect, resulting in 72 % isolated yield when acetanilide is used as the substrate (Table 1, entry 5). Fujiwara and coworkers showed that the acidity of the solvent can have a large influence on the reaction rate in their Pd(II)-catalyzed hydroarylation of alkenes, CF₃COOH being much more effective than HOAc. These observations were explained in terms of greater electrophilicity of the Pd(II) center when OAc[−] was replaced by CF₃COO[−], resulting in faster metalation of the aromatic C–H bond [9]. In our work, employing CF₃COOH as solvent (without added TsOH) results in similar catalyst performance to HOAc/TsOH (Table 1, entry 7).

Addition of inorganic acids (HCl, H₂SO₄) has a large detrimental effect on catalyst performance. Apparently, halides block the catalytic cycle by coordinating to the Pd(II) center, thereby reducing its electrophilicity (entry 8). Furthermore, the presence of halide anions can favor protonolysis of Pd–alkyl bonds over β-H elim-

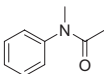
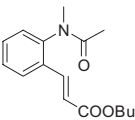
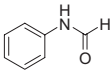
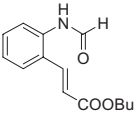
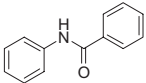
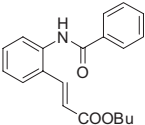
ination, as was studied by Zhang et al. [10]. The role of halide ions as a ligand were studied in stoichiometric reactions of arylpalladium reagents and Pd(II)-catalyzed reaction of phenylmercuric acetate with a variety of allylic compounds. The halide ion was found to inhibit β -H elimination and to promote β -heteroatom elimination in acidic media. In this reaction a C-Pd intermediate with a β -heteroatom (including halogen, acetoxy, alkoxy, and hydroxyl groups) gives only the β -heteroatom elimination product in the presence of halide ions, and β -H elimination is effectively blocked [10].

Use of other oxidants, e.g. hydrogen peroxide (Table 1, entry 9) or Cu(II)(OAc)₂, give conversions that are significantly lower than when benzoquinone is used. The role of the BQ can be twofold. It serves as the oxidant, resulting in the formation of Pd(II) and hydroquinone. This reaction is known to be accelerated by acid [11]. In addition, BQ can act as a ligand, stabilizing the low-valent Pd species present during the catalytic cycle [12]. Addition of more than one equivalent of BQ does not improve the yield significantly.

Table 2. Coupling of substituted anilide derivatives with *n*-butyl acrylate using Pd(OAc)₂ in acetic acid.^a

Entry	Substrate	Product	Yield (%)
1			85
2			91
3			38 ^b
4			62
5			(29)

Table 2. Continued

Entry	Substrate	Product	Yield (%)
6		10 	18 0
7		11 	19 (26)
8		12 	20 55

^a Reactions performed as in Table 1, entry 5. Yields in parentheses were determined by GC

^b Determined by ¹H NMR

Substituents on the aromatic moiety of the acetanilide substrate substantially affect the efficiency of the coupling reaction (Table 2). As expected, ortho-substitution hampers the reaction. It has been reported that the palladation of ortho-substituted acetanilides does not occur [7] or occurs at elevated temperatures only [7b]. With *N*-*m*-tolylacetamide (**6**) the reaction efficiency is enhanced to give a 91 % yield of **14**. Interestingly, reaction of *N*-methylanilide (**10**) gave no conversion at all. Formanilide and benzanilide (entries 7, 8) can be applied, although the yields are low to moderate.

The reaction also exhibits a large electronic dependence. Competition experiments with a series of 4-substituted acetanilides showed that electron-rich arenes react significantly faster ($k_{\text{obs}}(\mathbf{5}) > k_{\text{obs}}(\mathbf{8}) \approx k_{\text{obs}}(\mathbf{3}) \gg k_{\text{obs}}(\mathbf{9})$), although linear Hammett plots could not be obtained. A kinetic isotope effect is observed for the reaction ($k_{\text{H}}/k_{\text{D}} = 3$). Studies performed by Ryabov et al. have revealed that stoichiometric reaction of $[(\text{C}_6\text{H}_4\text{NHC}(\text{O})\text{CH}_3)\text{Pd}(\text{II})(\text{OAc})]_2$ complexes with styrenes can be acid-catalyzed, and that protonation is likely to occur at the bridging acetate ligands [13]. This protonation is followed by alkene coordination and then rate-limiting insertion of alkene into the palladium-carbon bond. We tested the dimeric *ortho*-palladated anilide complexes in the reaction with *n*-butyl acrylate and found that the rate of the reaction is at least an order of magnitude higher when using the preformed complexes compared with the catalysts generated in situ. These results suggest a reaction pathway via slow electrophilic attack of cationic $[\text{PdOAc}]^+$ species on the π -system of the arenes [5].

1.3.2.6.4 Additives

Heteropolyoxametalates are often used in combination with palladium salts as catalysts in oxidation processes using dioxygen as the oxidant. Indeed, the oxidative coupling reaction of benzenes with alkenes was also successfully achieved by use of the $\text{Pd}(\text{OAc})_2$ /molybdovanadophosphoric acid (HPMoV)/ O_2 system [14a]. For example, reaction of benzene with ethyl acrylate using this catalytic system in acetic acid afforded ethyl cinnamate as a major product in satisfactory yield. Typically, the reaction is conducted in acetic acid at 90 °C under 1 bar of O_2 . After 6 h the TON is 15. This number was recently improved to 121 [14b].

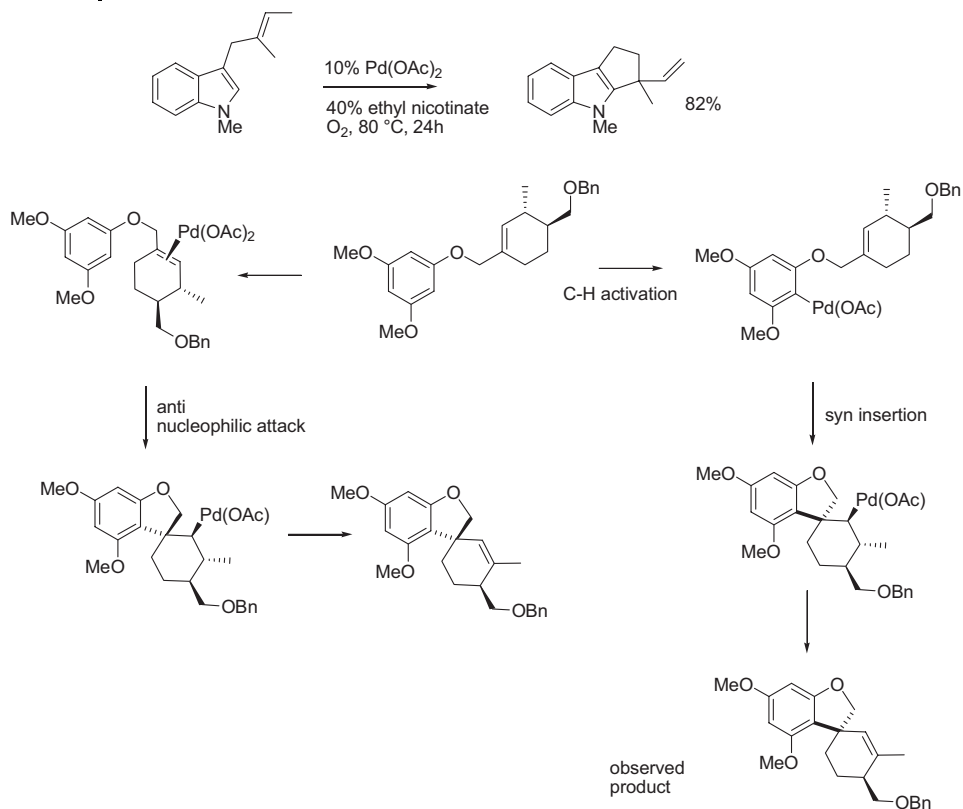
In a recent review it was argued that such additives of copper, benzoquinone, and HPMOV are not really needed; all that is needed is the presence of oxidation-resistant ligands that prevent palladium metal formation [15]. Indeed, activation of the C–H bond is not as slow as, for example, the Wacker reaction of ethene in which reoxidation of palladium must be performed by copper oxidation, although in this catalytic system the additives may still play a role in stabilizing the intermediate low-valent palladium species and thus prevent catalyst decomposition. This thesis was corroborated by the work of de Vos and Jacobs, who showed that addition of benzoic acid to the oxidative arylation reaction in the presence of oxygen led to superior results in the coupling of a variety of substituted arenes with acrylates, cinnamates, and α,β -unsaturated ketones. Very good yields and TON up to 762 were obtained at 90 °C. A mixture of the o, m, and p isomers is obtained if substituted arenes are used [16].

1.3.2.6.5 Intramolecular Reactions

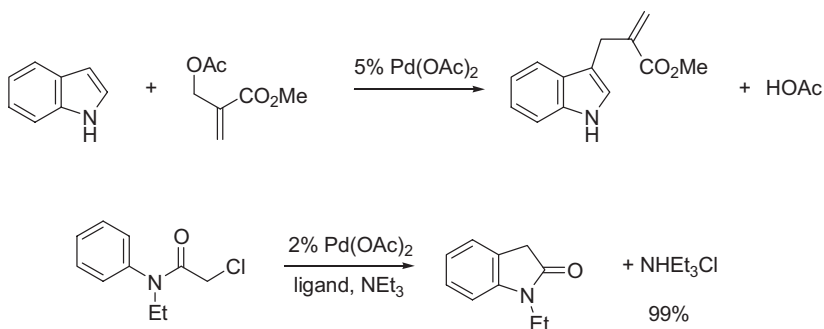
In an intramolecular version, oxidative coupling of indoles carrying butenyl groups at the 3-position resulted in cyclization to give annulated derivatives (Scheme 4) [17]. Stoltz reported use of oxygen or benzoquinone as the most effective oxidants, ethyl nicotinate as a stabilizing agent (perhaps as a ligand), and 10 % of palladium acetate as the catalyst. Turnover numbers are modest but, interestingly, the use of chiral centers in the side chain leads to stereospecific conversions with the formation of quaternary, chiral carbon centers. Likewise, allyl aryl ethers of electron-rich arenes lead to benzofurans (Scheme 4) [18]. Because the arene is very electron-rich one might consider a different mechanism – nucleophilic attack of the arene at the alkene activated by coordination to palladium. The stereospecificity of such a reaction was used to show that the reaction indeed involves C–H activation as the first productive step.

1.3.2.6.6 Recent Developments

A few recent examples of related C–C bond-forming reactions, all involving a palladium-catalyzed C–H activation step at arenes, will be mentioned. Salts are produced in these reactions, or acetic acid, as in the first example. Allylation of indoles at the 3-position was achieved by using palladium acetate, and bipyridine and allylic acetates as the reactants (Scheme 5) [19].



Scheme 4. Annulation of indole and the stereochemistry of oxidative dihydrobenzofuran formation.

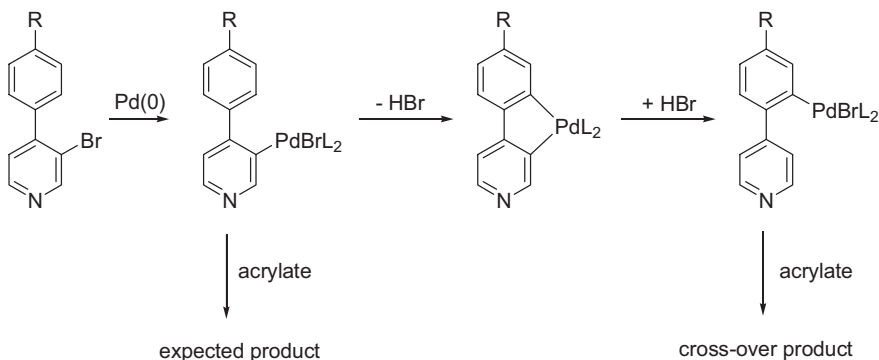


Scheme 5. C–H transformations not requiring oxidants, with acid or salt formation.

The cyclization of α -chloroacetanilides reported by Buchwald may also involve C–H activation (also Scheme 5). As mentioned above, acetanilides are among the most reactive substrates in this reaction. The presence of a base (Et₃N), and 2-PhC₆H₄PBu₂ as the ligand, are conditions more typical of cross-coupling of halides and therefore the sequence may start this way, followed by intramolecular

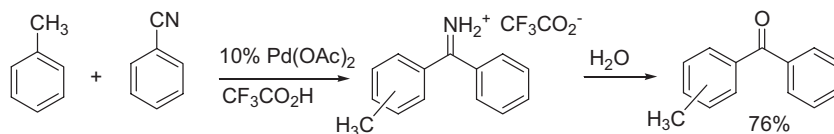
C–H activation. Turnovers up to 50 were achieved [20]. The cyclization is highly regioselective, obviating the need for prefunctionalized arenes.

A normal Heck reaction, thus producing salt, may be accompanied by an additional C–H activation step, as found by Gallagher et al. [21]. Biaryl bromides undergo the Heck reaction to give both the expected products (“retention”) and “crossover” products derived from migration of palladium and net transfer of reactivity from one aryl ring to the other (Scheme 6). Under the conditions used crossover is increasingly favored when electron-deficient arenes are involved. Crossover products derived from transfer on to the pyridine ring have also been observed.



Scheme 6. “Cross-over” via intramolecular C–H activation.

A reaction involving C–H activation requiring neither reoxidation nor salt separation has been reported by Larock (Scheme 7) [22]. Addition to nitriles of arylpalladium intermediates obtained via C–H activation gives palladium ketimides which react with acid to regenerate palladium salt, the catalyst, and ketimines (or their protonated conjugates). The co-produced ammonium trifluoroacetate formed after hydrolysis to liberate diaryl ketones does require regeneration. The maximum turnover number was 7. The example shows that in the absence of β -hydrogen atoms, maintaining palladium in a divalent state is also a promising approach to new catalytic conversions.



Scheme 7. Diaryl ketones via C–H activation.

1.3.2.6.7 Conclusions

From the examples above we can conclude that palladium-catalyzed oxidative vinylation of arenes has developed well beyond its inception by Fujiwara in the sixties. Quite good turnovers with O_2 as oxidant have now been achieved by use of addi-

tives such as benzoic acid. Although the reaction itself is not regioselective, leading to ortho, meta, and para mixtures with substituted benzenes, use of donating groups on the arene can induce highly selective orthometalation reactions leading to single products. Intramolecular versions are also high selective. Although some mechanistic work has been performed [23] the picture is not entirely clear. The need for additives such as benzoquinone, benzoic acid or ethyl nicotinate suggests that even under these oxidative conditions Pd(0) may form, leading to the formation of clusters that need stabilization to prevent formation of palladium black. This reaction is an obvious example of green chemistry, water being the only side-product. Thus, one can hope that in the near future this chemistry will be used for ton-scale production. In contrast, the alkylation reaction is much less well-developed. Here, the limitation would seem to be the choice of leaving group, because many leaving groups may inhibit the catalysis. We expect many new developments in these areas.

Experimental

General Procedure for Coupling Acetanilide Derivatives to *n*-Butyl Acrylate

In a typical experiment, 3.0 mmol anilide, 13.5 mg (0.06 mmol) Pd(OAc)₂, 324 mg (3.0 mmol) benzoquinone, and 286 mg (1.5 mmol) *p*-toluenesulfonic acid monohydrate are weighed into a one-necked round-bottomed flask equipped with a stirring bar. Next, 4.5 mL acetic acid is added, followed by a solution of 0.42 mL (3.0 mmol) *n*-butyl acrylate in 2.25 mL toluene. The flask is capped with a rubber septum and the mixture is stirred overnight. Samples of the mixture are taken, diluted with diethyl ether, washed with a saturated NaHCO₃ solution, dried over MgSO₄, and analyzed by GC or GC–MS. After 16 h the reaction mixture is diluted with 15 mL ether and carefully neutralized with 2.5 M NaOH solution. After extraction of the aqueous phase with 15 mL ether the combined organic phases are washed with water (15 mL), dried (MgSO₄), and evaporated in vacuo. The resulting solids are purified by column chromatography to yield the corresponding product as a white powder.

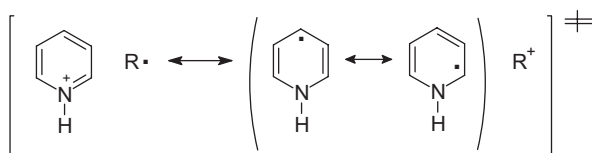
1.3.3

Minisci Radical Alkylation and Acylation

Ombretta Porta and Francesco Minisci

1.3.3.1 Introduction

The Friedel–Crafts alkylation and acylation are of very little, if any, synthetic interest when applied to heterocyclic aromatic bases; the substitution of protonated heterocycles by nucleophilic carbon-centered radicals is instead successful. This reaction, because of the dominant polar effect which is mainly related to the charge-transfer character of the transition state (Scheme 1), reproduces most of the aspects of the Friedel–Crafts aromatic substitution, but reactivity and selectivity are the opposite.



Scheme 1. Charge-transfer character of the transition state.

The parallelism with the Friedel-Crafts aromatic substitution arises because the more stable the carbocation, the more nucleophilic the corresponding radical will usually be. Thus, in principle, all the electrophilic species employed in the Friedel-Crafts reaction, when used as the corresponding radicals, should behave as nucleophiles in the selective substitution of heteroaromatic bases.

This reaction [1] is of synthetic interest for several reasons:

1. almost all carbonyl ($R-\dot{C}=O$, $RO-\dot{C}=O$, $RNH-\dot{C}=O$) and alkyl radicals without electron-withdrawing groups directly bonded to the radical center can be successfully introduced;
2. a wide variety of simple and cheap sources of these radicals are available starting from several of the most important classes of organic compounds;
3. all heteroaromatic bases (pyridines, quinolines, isoquinolines, acridines, diazines, benzodiazines, triazines, imidazoles, benzoimidazoles and benzothiazoles) and compounds of great biological interest (nucleosides, purines, and pteridines) with at least an α or γ position free are suitable substrates, and when all these positions are functionalized, ipso-substitution has occasionally been observed;
4. the reaction is highly chemo- and regioselective – substitution usually occurs at α and γ positions only.

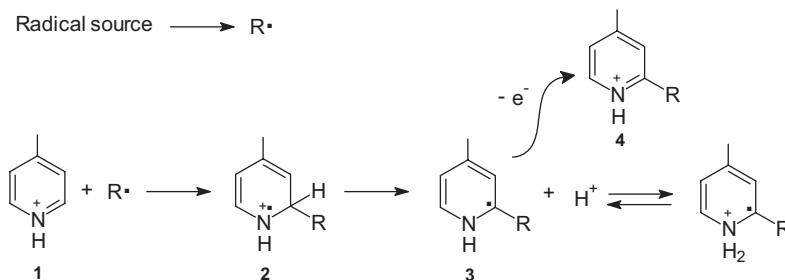
Several reviews [2] have been published, covering the overall synthetic and mechanistic evolution of the reaction, starting from 1973.

1.3.3.2 Mechanism

The general reaction mechanism is shown in Scheme 2. The high rate constants (from 10^5 to $10^8 \text{ M}^{-1} \text{ s}^{-1}$) for addition of nucleophilic radicals to protonated heterocycles [3] reduce other possible competitive side reactions of the radicals involved, strongly contributing to the synthetic interest.

With unprotonated heterocyclic bases, nucleophilic radicals either do not react (*t*-alkyl, benzyl, acyl, α -oxoalkyl, α -*N*-amidoalkyl) or react more slowly (3 to 6 orders of magnitude less) leading poor synthetic value (low yields and low chemo- and regioselectivity).

According to the FMO theory, the LUMO of the pyridinium cation has the highest coefficients at the carbon atoms in the α and γ positions and the dominant interaction in the radical addition occurs between the SOMO of the nucleophilic radical and the LUMO of the protonated heteroarene [3]. The rearomatization step of the radical cation **2** is very effective. In line with the mechanism of Scheme 2,



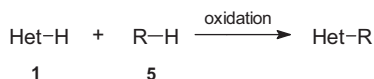
Scheme 2. Reaction mechanism of homolytic heteroaromatic substitution.

adduct 2 irreversibly loses a proton from the α C–H position affording the pyridinyl radical 3, which being a weaker base (pK_a 2–3) than the corresponding dihydropyridine ($pK_a \approx 7$) has an high equilibrium concentration in not strongly acidic medium. Because α -aminoalkyl radicals are good reducing agents with ionization potentials (~ 5 eV) close to those of Li and Na, very mild oxidants, for example Ti(IV) [4], can rapidly and selectively oxidize pyridinyl radicals 3 to the final rearomatized product 4. A great variety of thermal, photochemical and redox radical sources has been successfully utilized [2].

1.3.3.3 Scope, Limitations and Fundamental Examples

1.3.3.3.1 Radical Sources Involving Simultaneous Transformations at sp^2 and sp^3 -Hybridized Carbon Atoms

A quite general method of synthesis is depicted in Scheme 3, in which heterocyclic aromatic C–H and aliphatic C–H transformations are simultaneously involved.



Scheme 3. Simultaneous sp^2 and sp^3 transformation.

1 is the protonated heteroaromatic base and 5 can be an alkane, alkene, alky-laromatic, alcohol, ether, aldehyde, amine, amide, etc. The oxidant is usually a species which generates oxygen- or nitrogen-centered radicals suitable for hydrogen abstraction from C–H bonds, e.g. O_2 , H_2O_2 , RO-OH, $(ArCOO)_2$, $ArCO_2\cdot OR$, $(ROO)_2CO$, $S_2O_8^{2-}$, NH_2OH , NH_2OSO_3H , R_2NCl , R_3NO , $PhI(OAc)_2/N_3^-$. The redox metal salt catalysis, particularly suitable for the general Scheme 3, involves the couples Fe(III)/Fe(II), Cu(II)/Cu(I), Ag(II)/Ag(I), Ti(IV)/Ti(III), Co(III)/Co(II), and Ce(IV)/Ce(III).

Fundamental examples are shown in Eqs (1)–(8) of Table 1.

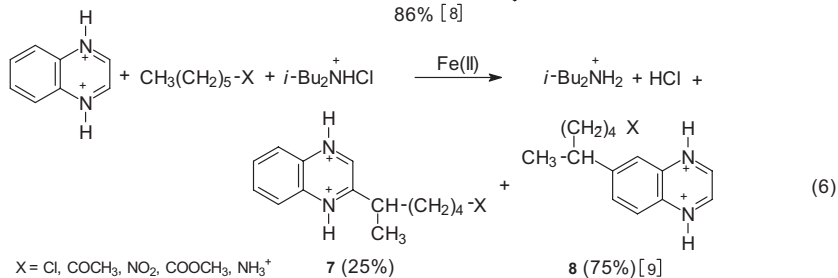
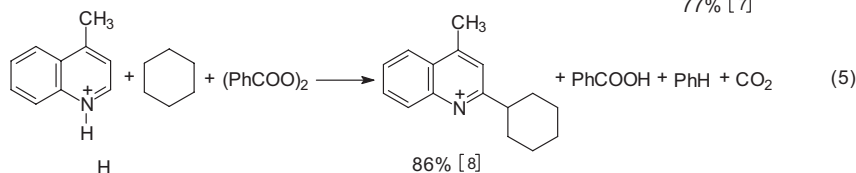
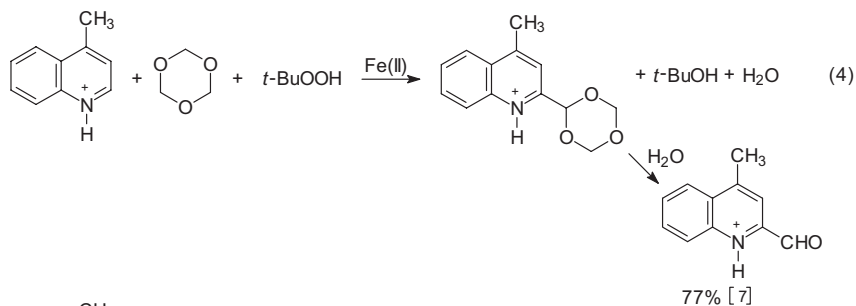
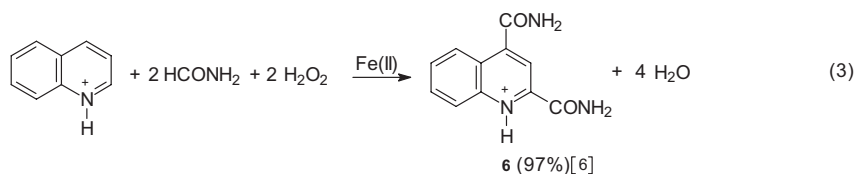
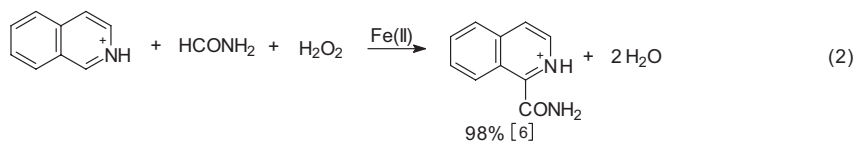
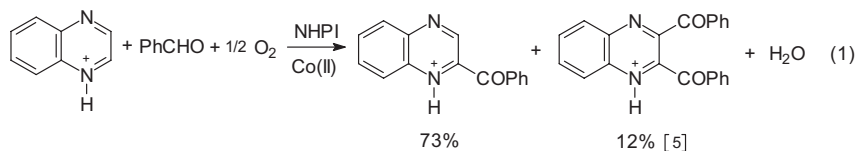
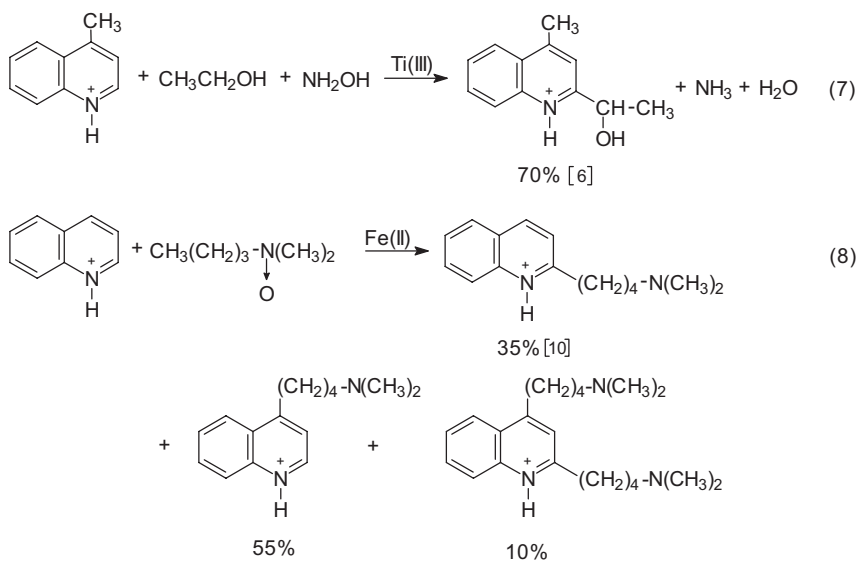
Table 1. Representative examples of simultaneous sp^2 and sp^3 transformation.

Table 1. Continued



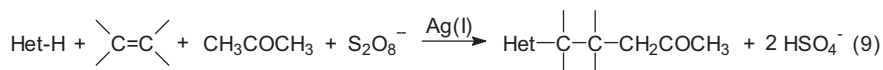
The yields reported in Eqs. (1)–(8) depend, with exception of Eqs. (6) and (8), on the starting heteroaromatic bases, but selectivity is higher because conversions are not always quantitative. Conversions can be increased by increasing the amounts of reagents. In Eq. (1) the aerobic oxidation is catalyzed by *N*-hydroxyphthalimide which generates the *N*-oxyl radical responsible for abstraction of hydrogen from benzaldehyde [5]. In Eqs. (2)–(4), the OH· and *t*-Buo· radicals, formed in classic Fenton-type processes, generate the nucleophilic radicals by hydrogen abstraction from formamide or *s*-trioxane. In Eq. (5) the Ph· and PhCOO· radicals abstract a hydrogen atom from cyclohexane producing the cyclohexyl radical. In Eq. (7) the NH₃⁺· radical, formed by Ti(III) reduction of ⁺NH₃OH, abstracts a hydrogen atom from ethanol generating the ketyl radical.

The regioselectivity observed in Eq. (6) with diprotonated quinoxaline (reaction performed in 96 % H₂SO₄) is of particular interest. Whereas in monoprotonated quinoxaline (Eq. 1) the C-2 carbon atom has the lowest electron density and substitution occurs at C-2 position only, in diprotonated quinoxaline (Eq. 6) the electron density of the equivalent C-2 and C-3 is as low as that of the equivalent C-6 and C-7 carbon atoms (NMR and INDO calculations) [9] and substitution occurs at both C-2 and C-6 positions. To minimize polysubstitution, the conversions in Eq. (6) were limited to about 50 % (selectivity, based on the reacted bases, is >90 % in any case). Another feature of Eq. (6) is the exceptional selectivity of hydrogen abstraction from the C-5 position of *n*-hexyl derivatives by the aminium radical *i*-Bu₂NH⁺, generated from *i*-Bu₂NHCl⁺ and Fe(II) [2].

A synthetic variation of the methodology reported in Eq. (6) is shown in Eq. (8), in which the selective intramolecular hydrogen abstraction by aminium radical

occurs. Results similar to those of Eq. (8) were obtained with *n*-hexyl-*N*-chloroamine and Fe(II). Noteworthy is the selective intramolecular hydrogen abstraction from the C–H at the 4-position (Eq. (8), entropic effect) versus the selective intermolecular hydrogen abstraction from the C–H at the 5-position (Eq. (6), polar and enthalpic effect) [2]. With diprotonated quinoxaline, substitution occurs at both C-2 and C-6-positions.

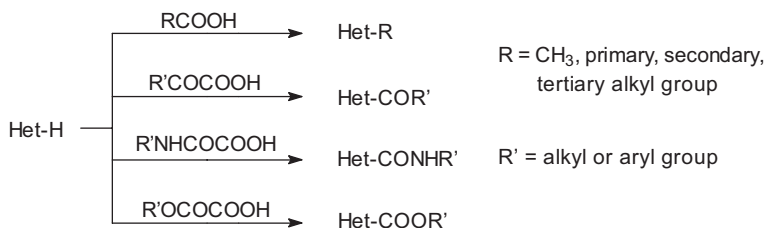
Another method consists in generating an electrophilic carbon-centered radical (e.g. the $\text{CH}_3\text{COCH}_2\cdot$ radical from acetone, peroxydisulfate and Ag(I)) which, instead of reacting with the protonated heteroarene, readily adds to simple alkenes forming a radical adduct that, owing to its nucleophilic character, selectively reacts with the heterocyclic ring (Scheme 4) [2].



Scheme 4. Heteroaromatic substitution by electrophilic radicals and alkenes.

1.3.3.3.2 Carboxylic Acids and Alcohols as Radical Sources

Carboxylic acids are the most general, versatile and useful source of carbon-centered radicals successfully used for selective alkylation and acylation of protonated heteroarenes. Alkyl, acyl, carbamoyl, and alkoxycarbonyl radicals have been obtained by oxidative decarboxylation of the corresponding acids with peroxydisulfate as an oxidant and Ag(I) as catalyst.



Scheme 5. Carboxylic acids as a sources of radicals.

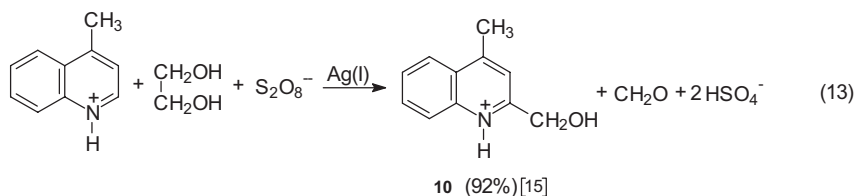
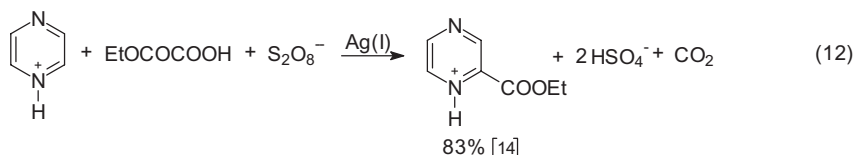
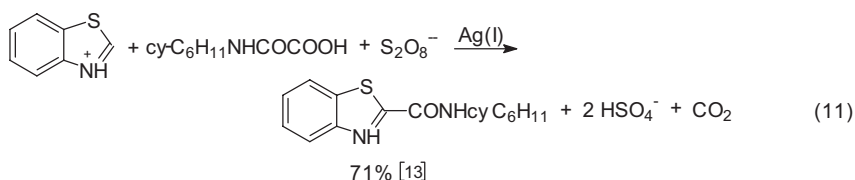
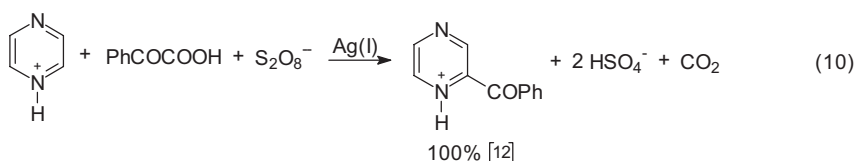
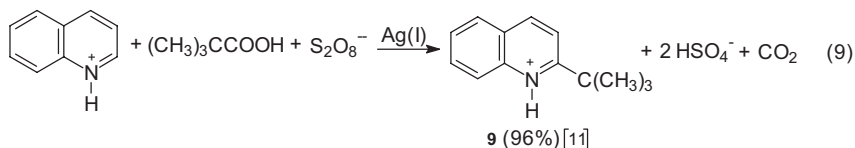
Several other processes have been developed, however, to accomplish the oxidative decarboxylation of carboxylic acids: oxidation by $\text{Pb}(\text{OAc})_4$, by iodosobenzene-diacetate, and by Ag(II) salt generated in situ in a catalytic cycle from a variety of peroxides (benzoyl peroxide, percarbonate, perborate) [2] other than the already mentioned peroxydisulfate. Representative examples are shown in Eqs (9)–(12) of Table 2.

The heteroaromatic substitution reflects the Friedel–Crafts reaction with the opposite reactivity and selectivity. The synthetic advantages and disadvantages are also opposite to those of concern for the selectivity of monosubstitution – whereas introduction of a carbonyl group deactivates the aromatic ring toward further substitution in the electrophilic process, in contrast it activates the heteroaromatic

ring in the homolytic reaction, favoring polysubstitution when the α and γ positions are free (Eq. 3); the opposite occurs in alkylation.

Selective monosubstitution with carbonyl-centered radicals is, however, possible by taking advantage of the reduced basicity because of introduction of a carbonyl group and use of a suitable acidic medium to make the starting base mainly protonated and the monosubstituted derivative much less protonated. The reac-

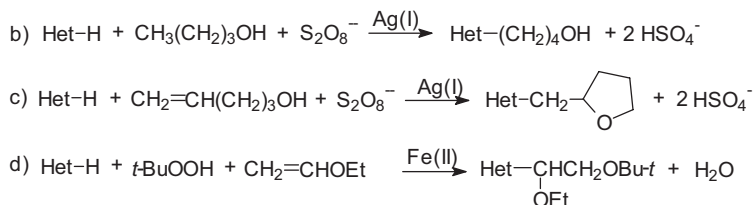
Table 2. Representative examples of acids and alcohols as radical sources.



tions in Eqs (10)–(12) were conducted in a two-phase system (i.e. $\text{H}_2\text{O}-\text{CH}_2\text{Cl}_2$) which favors monosubstitution by continuous extraction of the reaction products from the aqueous solution.

Conversions of the starting bases are almost quantitative for Eqs (9), (10), and (12) whereas for Eq. (11) it is 78 % (selectivity is >90 %).

Alcohols are not only source of ketyl radicals generated by hydrogen abstraction from the $\alpha\text{-C-H}$ position (Eq. (7), Table 1). Oxidation of alcohols with $\text{Pb}(\text{OAc})_4$, $\text{PhI}(\text{OAc})_2$, and $\text{S}_2\text{O}_8^{2-}$ with $\text{Ag}(\text{I})$ as catalyst produces alkoxy radicals ($\text{RO}\cdot$) which may further undergo β -scission (Eq. 13), intramolecular hydrogen abstraction, or intra- and intermolecular addition to alkenes, generating a nucleophilic carbon-centered radical useful for heteroaromatic substitution (Scheme 6) [2].



Scheme 6. Alcohols as sources of carbon-centered radicals in heteroaromatic substitution.

1.3.3.3.3 Alkyl Halides as Radical Sources

Alkyl iodides have been widely used for selective alkylation of heteroaromatic bases. The method is based on rapid iodine abstraction by aryl radicals (obtained from benzoyl peroxide or diazonium salts) or by a methyl radical (obtained from MeCOOH , $t\text{-BuOH}$, $t\text{-BuOOH}$, $(t\text{-BuO})_2$, $(\text{MeCOO})_2$, $\text{MeSOMe}/\text{H}_2\text{O}_2$, or $\text{MeCOMe}/\text{H}_2\text{O}_2$) [2]. An example is depicted in Eq. (14) of Table 3.

Perfluoroalkyl radicals are readily obtained by the same procedures but, owing to their electrophilic character, they are not suitable for selective heteroaromatic substitution. In the presence of simple alkenes, perfluoroalkyl radicals add very rapidly to the olefinic bond and the radical adduct, which has nucleophilic character, selectively reacts with the heterocyclic ring (Eq. 15).

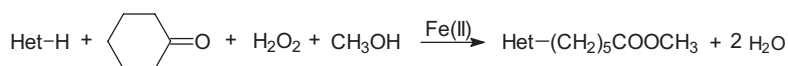
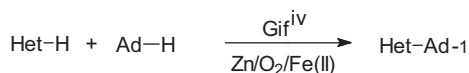
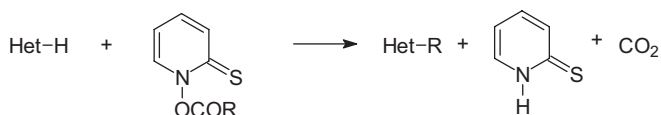
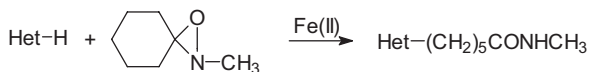
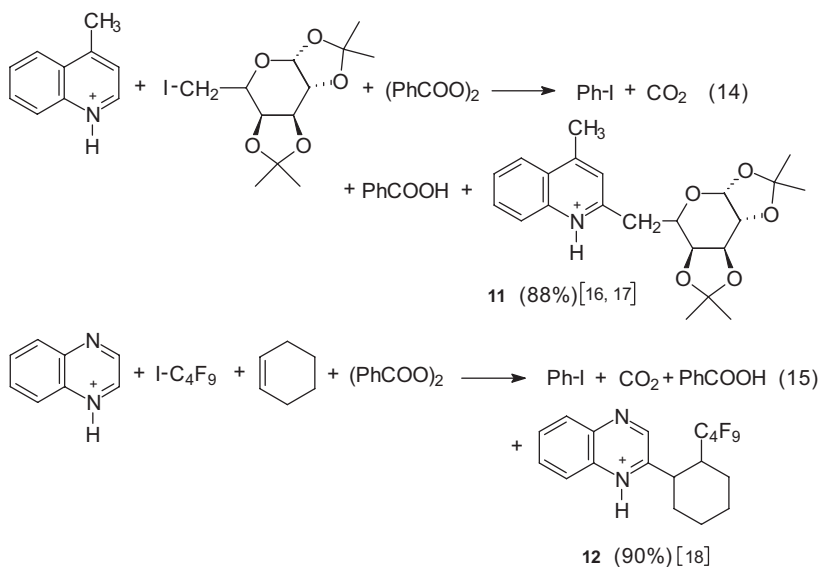
Alkyl bromides have also been used as sources of alkyl radicals for selective heteroaromatic alkylation by using Bu_3SnH in combination with azobisisobutyronitrile or a variety of silanes and peroxides (Scheme 7) [2].



Scheme 7. Alkyl bromides as sources of radicals in the heteroaromatic substitution

1.3.3.3.4 Various Sources of Radicals

A variety of different sources of radicals have been used in several heteroaromatic substitution reactions [2]; these include acyl peroxides, oxaziridines, thiohydroxamic Barton esters, the Gif reaction, alkyl xanthates, and ketones/ H_2O_2 (Scheme 8).

Table 3. Representative examples of alkyl iodides as sources of radicals.**Scheme 8.** Different sources of radicals for the heteroaromatic substitution.

Experimental

Quinoline-2,4-dicarboxamide [6] (**6**) (Eq. 3)

A solution of 10 mmol quinoline (1.3 g), 10 mmol H_2SO_4 , 25 mmol H_2O_2 and 0.3 mmol of $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ in 100 mL HCONH_2 was warmed, with stirring, for 4 h at 60 °C. The resulting solution was diluted with water and made basic with a 10 % NaOH solution. The solid formed was separated and the aqueous solution was extracted with CH_2Cl_2 . On work-up of the organic extract 2.21 g of a solid were obtained (m.p. 271–274 °C). GC analysis (with lepidine-2-carboxamide as internal standard) revealed 97 % yield of quinoline-2,4-dicarboxamide. On crystallization from EtOH the reaction product (m.p. 278–279 °C) was identical with an authentic sample of **6** (m.p., GC, ^1H NMR and MS).

Reaction of Quinoxaline with 1-Hexylamine and *N*-Chlorodiisobutylamine [9] (**7** and **8**, $\text{X} = \text{NH}_2$) (Eq. 6)

A solution of *N*-chlorodiisobutylamine (50 mmol) in 50 mL 96 % H_2SO_4 was added dropwise (3 h) with vigorous stirring at r.t. to a mixture of quinoxaline (50 mmol), finely powdered $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (5 mmol), and 1-hexylamine (150 mmol) in 60 mL 96 % H_2SO_4 . Additional $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (10 mmol) was added in portions during the reaction. After 2 h the solution was poured on to ice (500 g), made alkaline with a 12 M NaOH solution, extracted with CHCl_3 and analyzed by GC. Unreacted quinoxaline (50 %), isomer **7** (12 %), and isomer **8** (33 %) were subsequently isolated by flash column chromatography on silica gel (EtOAc–MeOH, 7:3). Isomer **7**: b.p. 150 °C (0.5 mmHg); ^1H NMR (CDCl_3) δ 1.42 (d, 3H, CH_3), 1.3–2.2 (m, 6H, $-(\text{CH}_2)_3-$), 3.17 (sext, 1H, CH), 3.42 (t, 2H, CH_2N), 7.7–8.2 (m, 4H, H-5, H-6, H-7, H-8), 8.76 (s, 1H, H-3); MS, m/e 248 (M^+), 213, 185, 171, 158, 144, 131. Isomer **8**: b.p. 160 °C (0.5 mmHg); ^1H NMR (CDCl_3) δ 1.40 (d, 3H, CH_3), 1.2–2.2 (m, 6H, $-(\text{CH}_2)_3-$), 2.97 (sext, 1H, CH), 3.43 (t, 2H, CH_2N), 7.65 (d, 1H, H-7), 7.90 (d, 1H, H-5); 8.10 (d, 1H, H-8), 8.82 (s, 2H, H-2, H-3); MS, m/e 248 (M^+), 213, 185, 171, 158, 144, 136.

2-*tert*-Butylquinoline (**9**) [11] (Eq. 9)

A mixture of 2.5 mmol quinoline, 7 mmol pivalic acid, 0.2 mmol AgNO_3 , 5 mmol $(\text{NH}_4)_2\text{S}_2\text{O}_8$, and 5 mmol H_2SO_4 in 25 mL of water and 25 mL of chlorobenzene was heated under reflux for 2 h. The aqueous solution was made basic with NaOH, the organic solvent was separated, and the aqueous solution was extracted with CH_2Cl_2 . GC analysis of the organic extract (with quinaldine as internal standard) revealed the presence of 2.4 mmol **9** and 0.1 mmol unreacted quinoline. Compound **9** was isolated as pure liquid by flash column chromatography on silica gel (hexane–EtOAc, 6:1). ^1H NMR (500 MHz, CDCl_3) δ 1.51 (s, 9H, 3CH_3), 7.28 (d, 1H, $J=8.2$ Hz, H-3), 7.50 (1H, ddd, $J=1.4, 6.8, 8.2$ Hz, H-6), 7.70 (1H, ddd, $J=1.4, 6.9, 8.3$ Hz, H-7), 7.79 (1H, dd, $J=1.6, 8.3$ Hz, H-5), 8.06 (1H, d, $J=8.3$ Hz, H-8), 8.09 (1H, d, $J=8.3$ Hz, H-4); MS, m/e 185 (M^+), 170, 155, 125.

2-Hydroxymethyllepiline (10) [15] (Eq. 13)

A solution of 20 mmol lepiline, 20 mmol CF_3COOH , 80 mmol $(\text{NH}_4)_2\text{S}_2\text{O}_8$, and 2 mmol AgNO_3 in 75 mL water and 75 mL $(\text{CH}_2\text{OH})_2$ was heated under reflux for 3 h. The aqueous solution was made basic with NaOH and extracted with CH_2Cl_2 . GC analysis (with quinoline as internal standard) of the organic extract revealed the presence of 1.3 mmol unreacted lepiline and 18.5 mmol **10**. Flash column chromatography on silica gel (hexane–EtOAc, 2:1) gave 17.1 mmol pure **10**: m.p. 85 °C; ^1H NMR (CDCl_3) δ 2.60 (s, 3H, 4- CH_3), 4.91 (s, 2H, CH_2O), 7.16 (s, 1H, H-3), 7.4–7.7 (m, 2H, H-5 and H-7), 7.9–8.1 (m, 2H, H-6 and H-8); MS, m/e 173 (M^+), 144, 128, 115.

6-Deoxy-6-(4'-methyl-2'-quinolyl)-1,2:5,6-di-O-isopropylidene- α -D-galactopyranose (11) [16] (Eq. 14)

A solution of 10 mmol lepiline, 15 mmol iodosugar, 27 mmol $(\text{PhCOO})_2$, and 15 mmol CF_3COOH in 100 mL of CH_3CN was heated under reflux for 8 h. The solution was poured into cold 10 % aqueous Na_2CO_3 solution and extracted with CH_2Cl_2 . After evaporation of the solvent, 8.1 mmol of **11** were isolated as a liquid by flash column chromatography on silica gel (EtOAc–hexane, 6:4): ^1H NMR (300 MHz, CDCl_3) δ 1.25, 1.35, 1.55 (3s, 3H, 3H, 6H, C- CH_3), 2.70 (s, 3H, Het- CH_3), 3.15–3.30 (m, 2H, H-6a, 6b), 4.29 (dd, 1H, H-4, $J_{4-5} = 1.5$ Hz, $J_{3-4} = 7.5$ Hz), 4.31 (dd, 1H, H-2, $J_{1-2} = 5.0$ Hz, $J_{2-3} = 2.5$ Hz), 4.59 (m, 1H, H-5), 4.64 (dd, 1H, H-3), 5.47 (d, 1H, H-1), 7.25 (s, 1H, H-3'), 7.4–7.7 (2t, 2H, H-5', H-6'), 7.9–8.1 (2d, 2H, H-7', H-8'); MS, m/e 385 (M^+ , 45), 370 ($\text{M}^+ - 15$, 60), 298 (100), 157 (95); HRMS 385.188 (calcd for $\text{C}_{22}\text{H}_{25}\text{NO}_5$, 385.189).

Reaction of Quinoxaline with Perfluoro-*n*-butyl Iodide and Cyclohexene (12) [18] (Eq. 15)

A solution of 2 mmol quinoxaline, 4 mmol cyclohexene, 3 mmol perfluoro-*n*-butyl iodide, 2 mmol CF_3COOH , and 3 mmol benzoylperoxide in 10 mL CH_3COOH was heated under reflux for 6 h. On removal of CH_3COOH under vacuum, a solution of 10 % aqueous NaOH was added and the mixture was extracted with EtOAc. Compound **12** was isolated by flash column chromatography on silica gel (hexane–EtOAc, 95:5) (1.8 mmol, 90 %): ^1H NMR (500 MHz, CDCl_3) δ 1.37–1.63 (m, 4H), 1.69–2.04 (m, 3H), 2.20 (m, 1H, H-3/H-6), 3.14–3.30 (m, 2H, H-2 and H-1), 7.70 (ddd, 1H, $J = 1.7, 7.0, 8.3$ Hz, H-7'/6'), 7.74 (ddd, 1H, $J = 1.7, 7.0, 8.3$ Hz, H'-6'/7'), 8.03 (dd, 1H, $J = 1.7, 8.3$ Hz, H-8'/5'), 8.08 (dd, 1H, $J = 1.7, 8.3$ Hz, H-5'/8'), 8.71 (s, 1H, H-3'); ^{19}F NMR (470 Hz, CFCl_3) –127.1 (dm, 1F, $^2J = 293$ Hz), –124.7 (dm, 1F, $^2J = 293$ Hz), –121.6 (dm, 1F, $^2J = 296$ Hz), –120.2 (dm, 1F, $^2J = 296$ Hz, $^3J = 12$ Hz, $\text{F}_\beta\text{-F}_\gamma$), –117.5 (d, 1F, $^2J = 281$ Hz, F_α), –104.7 (d, 1F, $^2J = 281$ Hz, F_α), –80.8 (t, 3F, $J = 9.0$ Hz, F_γ); MS, m/e 430 (M^+), 411 ($\text{M}^+ - \text{F}$), 157, 144, 129, 69, 57, 43.

1.4

Aryl–Aryl Coupling Reactions

1.4.1

Intermolecular Arylation Reactions

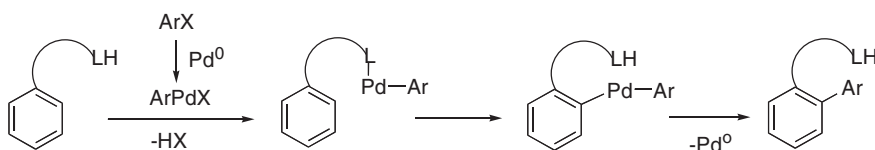
1.4.1.1 Intermolecular Arylation Reactions of Phenols and Aromatic Carbonyl Compounds

Masahiro Miura and Tetsuya Satoh

1.4.1.1.1 Introduction

Transition metal-catalyzed cross-coupling is now recognized to be one of the most powerful carbon–carbon bond-formation reactions [1]. The palladium-catalyzed coupling of aryl halides or their synthetic equivalents, for example aryl triflates, with arylmetals is very often employed in the synthesis of biaryl molecules, whose skeletons are found in a wide range of important compounds including natural products and organic functional materials [1–3].

Appropriately functionalized aromatic substrates such as phenols and aromatic carbonyl compounds have recently been found to undergo intermolecular arylation directly and regioselectively on treatment with aryl halides in the presence of transition metal catalysts such as Pd, Rh, and Ru [3, 4] (for intramolecular reaction, see Chapter III.1.4.2). As illustrated in Scheme 1, which is a general catalytic sequence with palladium, coordination of a given functional group to a metal center is the key to effective coupling by C–H bond cleavage. Clearly the reaction has a significant advantage – the stoichiometric metalation of aromatic substrates is not required. Representative examples and some related reactions are summarized in this section.

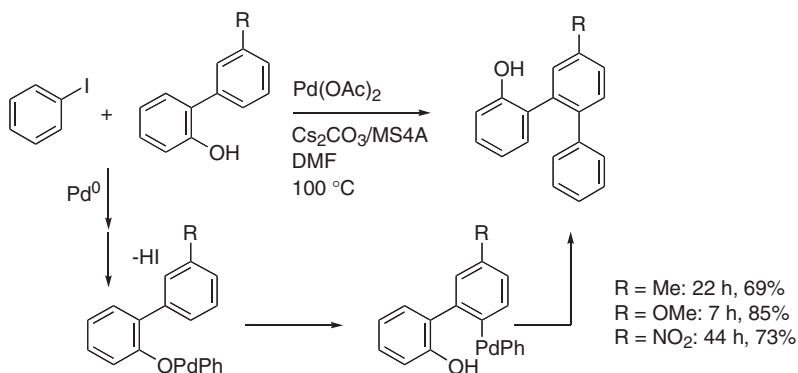


Scheme 1. Pd-catalyzed and coordination-assisted intermolecular aryl-aryl coupling via C–H bond cleavage

1.4.1.1.2 Reaction of Phenols

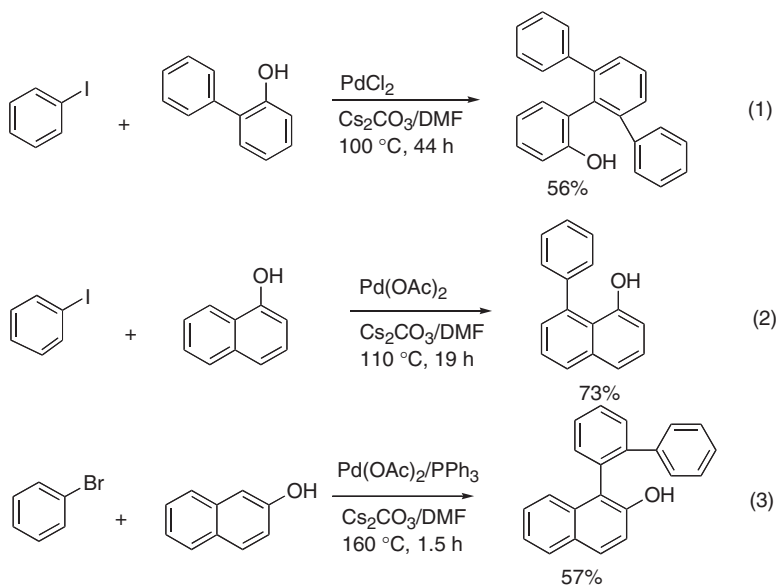
Arylation of 2-phenylphenols with aryl iodides (Scheme 2) is one of the first examples to proceed by the sequence given in Scheme 1 [5, 6]. The reaction proceeds via (1) oxidative addition of iodobenzene to Pd⁰ to give PhPdI, (2) coordination of the phenolic oxygen to Pd, (3) palladation at the 2'-position to form a diarylpalladium intermediate, and (4) reductive elimination of the product. The use of a relatively strong inorganic base, for example Cs₂CO₃, is important for a smooth coupling. K₂CO₃ and Na₂CO₃ are less effective, in this order. Aromatic palladation via C–H bond cleavage may involve a Friedel–Crafts type electrophilic substitution or

oxidative addition[7]. That the reactions of substrates with an electron-donating substituent in the 5'-position proceed smoothly seems to be consistent with the former mechanism. The strongly electron-withdrawing nitro group does not inhibit the reaction, however. Although the mechanism is not definitive, these results may imply that both pathways may participate in the reaction. Anyway, the base appears to promote the reaction effectively.

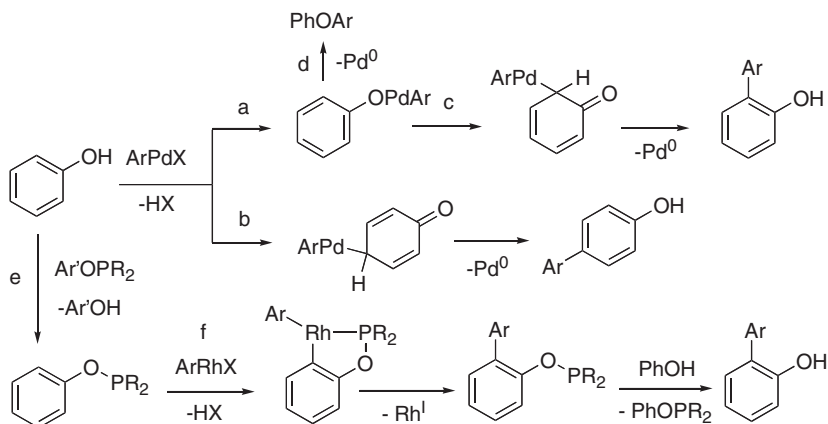


Scheme 2. Pd-catalyzed regioselective arylation of 2-phenylphenols.

Simple 2-phenylphenol with less steric restriction can undergo diarylation to give a sterically congested 1,2,3-triphenylbenzene derivative (Eq. 1). 1-Naphthol is arylated at the peri position selectively (Eq. 2). Interestingly, 2-naphthol undergoes successive diarylation on treatment with bromobenzenes in the presence of PPh₃

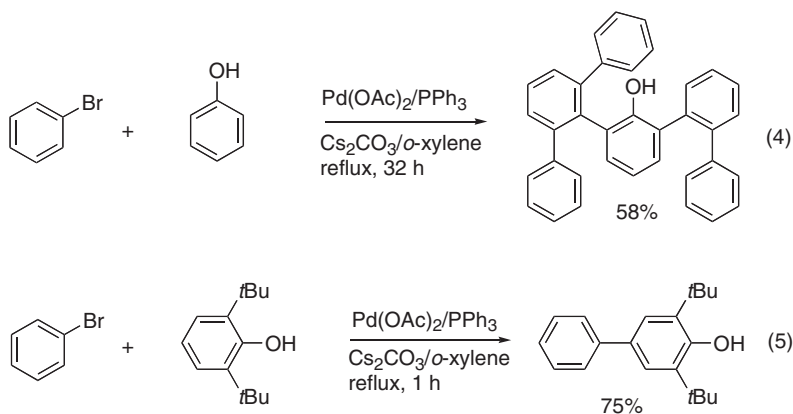


as ligand (Eq. 3). The reaction is believed to involve two different mechanisms. The first arylation at the 1-position may occur in a similar sequence to the α -arylation of ketones via enolates (paths a and c in Scheme 3) [4, 9]. The second may proceed in the same manner with the reaction in Scheme 2.

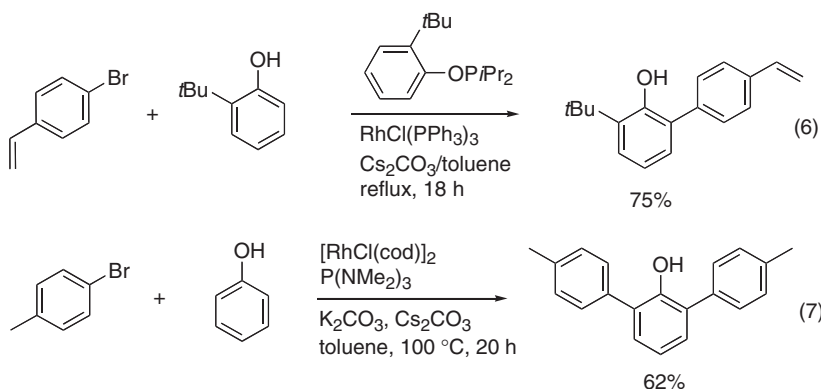


Scheme 3. Possible mechanistic sequences for the catalytic arylation of phenol.

Phenol itself can be arylated multiply around the oxygen up to five times by use of excess bromobenzene (Eq. 4) [8]. The use of a less polar solvent such as *o*-xylene is important; no reaction of phenol occurs in DMF. The lack of hexa-arylated product may be attributed to steric reasons. When the 2- and 6-positions of phenol are masked by *tert*-butyl groups, the 4-position is arylated (Eq. 5) and path b in Scheme 3) [10]. It is worth noting that a diaryl ether is formed by reductive elimination of the alkoxyarylpalladium intermediate when a bulky phosphine ligand is used (path d) [11].

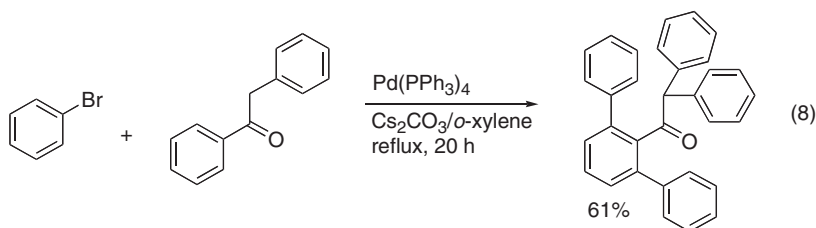


The ortho arylation of phenols with aryl bromides has also been found to occur when rhodium catalysts are used [12–14]. The key to the reaction is to employ phosphinites or phosphites as ligands. An example using a phosphinite ligand is given in Eq. (6) [13]. The reaction is believed to proceed by coordination of a phosphinite to ArRh(III) generated by oxidative addition (paths e and f); this is followed by cyclometalation and reductive elimination. The arylated phosphinite then undergoes transesterification with the starting phenol to give the product. In this reaction a phosphinite having the same aryloxy group as the phenol substrate must be prepared. This can, however, be avoided by using $\text{P(NMe}_2)_3$, which reacts with phenols in situ to give the corresponding phosphites (Eq. 7) [14]. It is noted that under the rhodium-catalyzed conditions no Heck type reaction occurs (Eq. 6) and minor amounts of the products arylated at the 2'-position, as in the palladium-catalyzed reaction (Scheme 2), are observed.

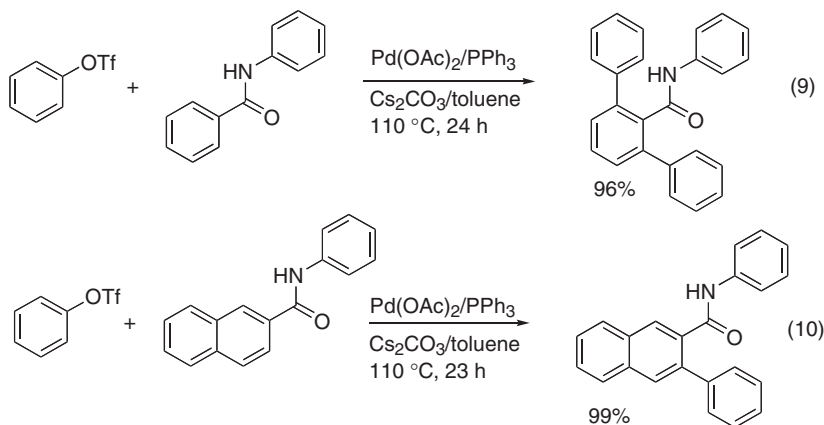


1.4.1.1.3 Reaction of Aromatic Carbonyl Compounds and Related Substrates

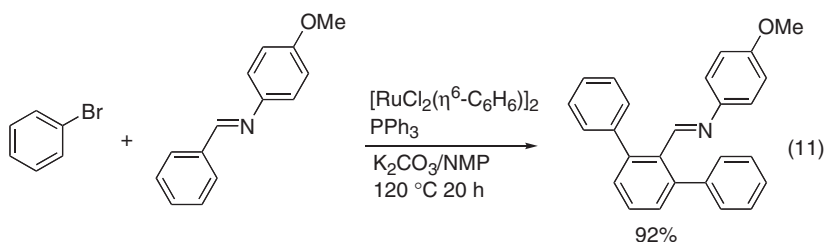
Alkyl aryl ketones are known to be arylated at the α -position of the alkyl groups, via the corresponding enolates, by treatment with aryl halides in the presence of palladium catalysts [4, 9]. The ortho arylation of alkyl aryl ketones is also possible. For example, in the reaction of benzyl phenyl ketones with bromobenzenes, the arylation first occurs at the benzylic position; the ortho positions are then arylated via C–H bond cleavage (Eq. 8) [15]. The ortho arylation is believed to occur after coordination of the enol oxygen to ArPd(II) , which is followed by ortho palladation as in the reaction of 2-phenylphenols shown in Scheme 2.



Benzanilides also undergo ortho arylation (Eqs. 9 and 10) [16]. For these reactions, aryl triflates as arylation reagents are more effective than aryl bromides. The reaction is also believed to proceed via coordination of amide anion to ArPd(II) , because no reaction occurs with secondary amides.

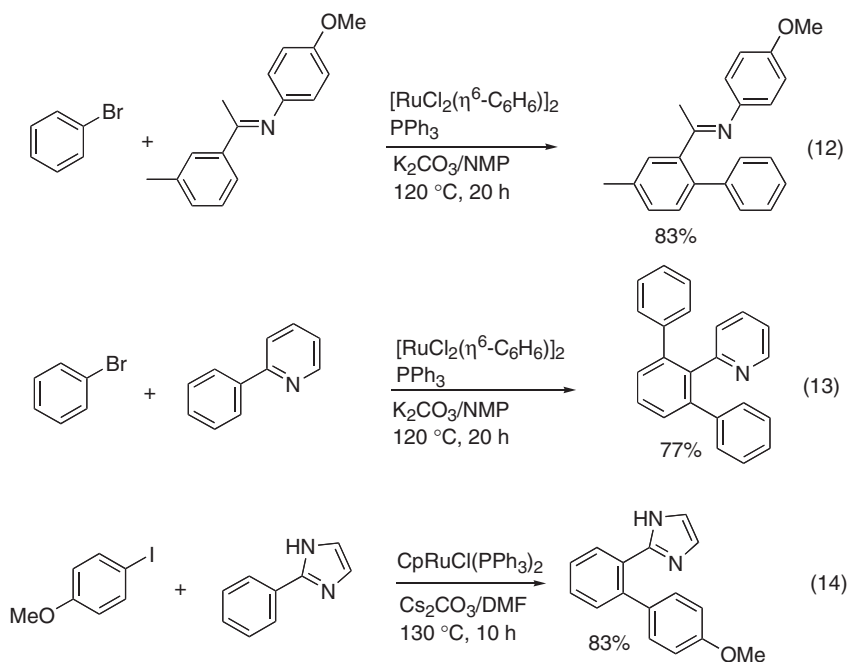


Benzylidene anilines formed from benzaldehydes and anilines have been found to undergo ortho arylation effectively when a ruthenium catalyst such as $[\text{RuCl}_2(\eta^6\text{-C}_6\text{H}_6)]_2$ is used in the presence of K_2CO_3 as base (Eqs. 11 and 12) [17]. A polar solvent such as NMP is used. In this reaction the substrates have no acidic hydrogen and thus ortho metalation seems to occur via coordination of the neutral nitrogen to the metal center, as in the reaction of phosphinite (Scheme 3). Similarly, 2-phenylpyridine [18] (Eq. 13) and 2-phenyl-1*H*-imidazole (Eq. 14) [19] are arylated.

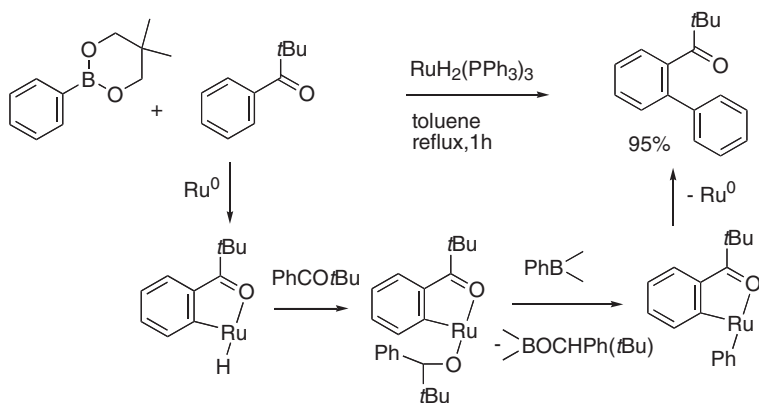


It should be noted that introduction of a substituent to these substrates at an appropriate position enables the exclusive formation of the mono-arylated product as represented by Eqs. (10) and (12) (see also Scheme 2). The use of a limited amount of arylating reagent is sometimes successful for obtaining mono-arylated product selectively. In the reaction of Eq. (14), the Cp ligand on the ruthenium catalyst is believed to enable selective mono-arylation [19].

Direct aromatic arylation with arylmetal reagents has also been developed. Alkyl aryl ketones undergo arylation on treatment with arylboronates in the pres-

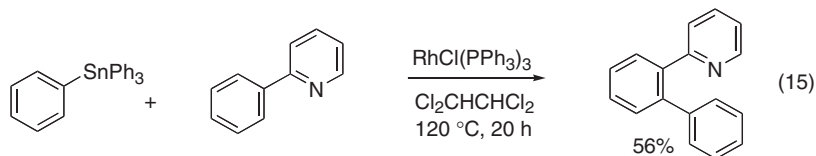


ence of a ruthenium catalyst (Scheme 4) [20]. As expected, depending on the bulkiness of the alkyl groups, either mono- or diarylation can be performed selectively. The reaction proceeds via initial C–H bond cleavage at the *ortho* position to give a metallacycle; this is followed by the reaction with another ketone molecule. Successive transmetalation and reductive elimination close the catalytic cycle. Thus, an equimolar amount of ketone is reduced during the reaction.



Scheme 4. Rhodium-catalyzed *ortho*-arylation of *t*-butyl phenyl ketone with 5,5-dimethyl-2-phenyl-[1,3,2]dioxaborinane.

2-Phenylpyridine is arylated by using aryltin reagents such as Ph_4Sn in the presence of a rhodium catalyst (Eq. 15) [21]. The use of a halogenated solvent is important for obtaining a satisfactory yield. Although the precise mechanism is not yet clear, it is likely that a cyclometalated intermediate participates.



Experimental

2,6-(Diphenyl)benzoylaniline (Eq. 9)

A mixture of benzanilide (197 mg, 1 mmol), phenyltriflate (904 mg, 4 mmol), $\text{Pd}(\text{OAc})_2$ (11.2 mg, 0.05 mmol), PPh_3 (78 mg, 0.3 mmol), Cs_2CO_3 (1.30 g, 4 mmol), and toluene (8 mL) was stirred under nitrogen at 110°C for 24 h. After cooling, the reaction mixture was poured into dilute HCl, extracted with ethyl acetate, and the extract was dried over sodium sulfate. Evaporation of the solvent and washing of the residual solid well with hexane gave product 2,6-(diphenyl)benzoylaniline (335 mg, 96%). m.p. $279\text{--}280^\circ\text{C}$; ^1H NMR (400 MHz, DMSO-d_6) δ = 6.95 (t, J = 7.3 Hz, 1H), 7.15 (t, J = 7.3 Hz, 2H), 7.20 (d, J = 7.3 Hz, 2H), 7.29 (d, J = 7.3 Hz, 2H), 7.36 (t, J = 7.3 Hz, 4H), 7.43 (d, J = 7.8 Hz, 2H), 7.50 (d, J = 7.3 Hz, 4H), 7.60 (t, J = 7.8 Hz, 1H), 10.14 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 120.01, 123.66, 127.46, 128.25, 128.53, 128.63, 129.06, 129.11, 136.49, 138.62, 139.53, 140.38, 166.76; MS m/z 349 (M^+).

1.4.1.2 Palladium-Catalyzed Arylation of Heteroarenes

Masahiro Miura and Tetsuya Satoh

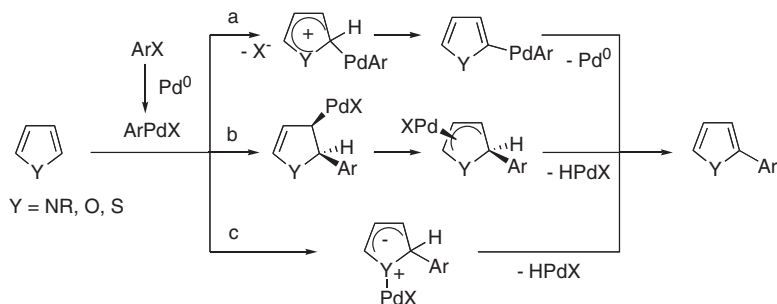
1.4.1.2.1 Introduction

As described in Section III.1.4.1.1, the catalytic direct arylation reactions of aromatic compounds occurs effectively via C–H bond cleavage when the substrates are appropriately functionalized. On the other hand, various five-membered heteroaromatic compounds involving one or two heteroatoms, even without a functional group, are known to undergo arylation, usually at their 2- and/or 5-position(s), on treatment with aryl halides under the action of palladium catalysis. The coupling has recently been developed significantly [1, 2]. Representative examples with some mechanistic discussion are summarized in this section.

1.4.1.2.2 Reaction of Pyrroles, Furans, and Thiophenes

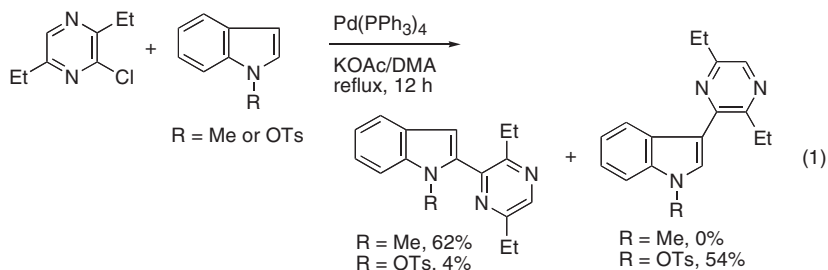
The arylation of these substrates, which are susceptible to electrophiles, may be regarded as proceeding through a Friedel–Crafts type mechanism involving attack of $\text{ArPd}(\text{II})$ species, as judged by the usual substitution pattern (path a in Scheme

1) [3]. However, either a Heck-type mechanism via carbopalladation (path b) or a coordination-assisted mechanism (path c) seems to be capable of taking part [4]. Thus, it is likely there is not one mechanism only and these pathways occur depending on the substituents on each nucleus and reaction conditions as described below.



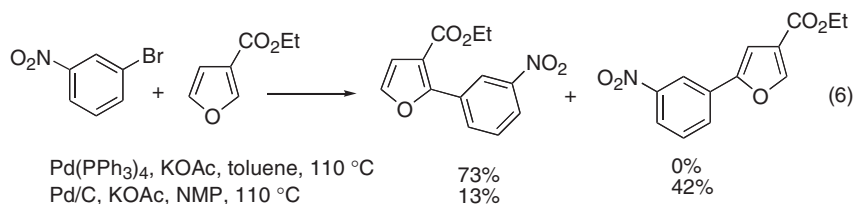
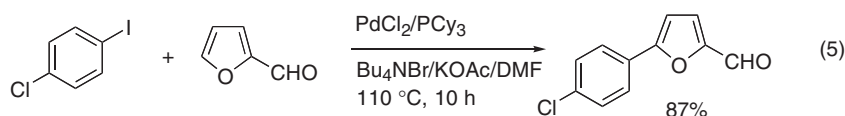
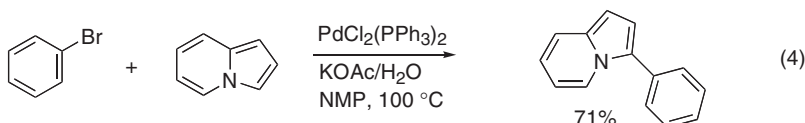
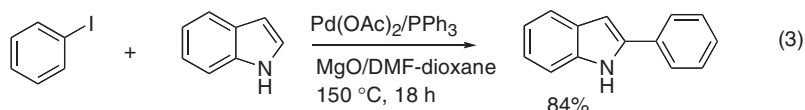
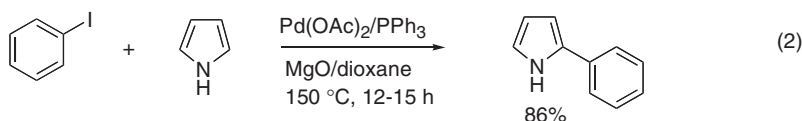
Scheme 1. Possible catalytic sequences for the Pd-catalyzed intermolecular arylation of five-membered heteroaromatic compounds involving one heteroatom.

An early significant example is the coupling of 1-substituted indoles with 2-chloro-3,6-dialkylpyrazines (Eq. 1) [5, 6]. Depending on the 1-substituents, the reaction occurs selectively at 2- or 3-position. Substitution at the 3-position is a rare occurrence and seems to be caused by the electron-withdrawing tosyl group, although the precise mechanism is still not clear.

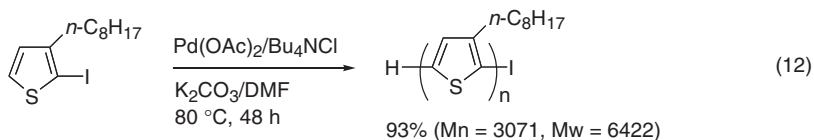
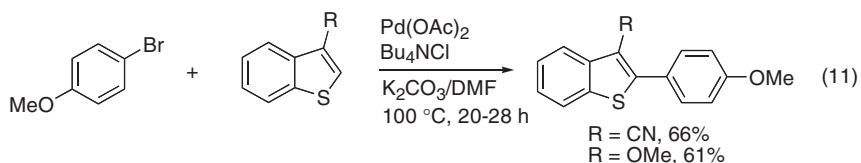
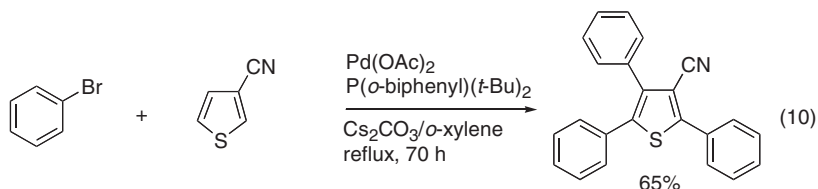
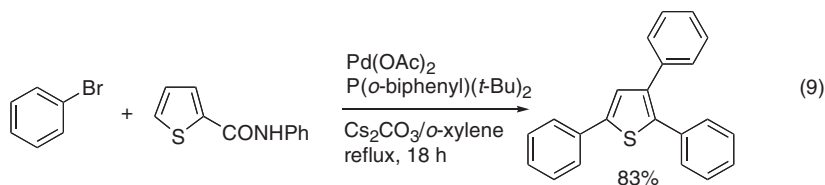
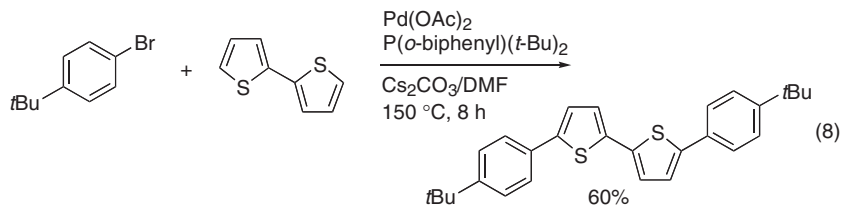
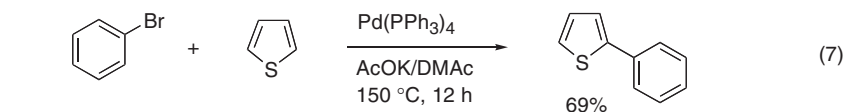


The reaction of pyrrole with iodobenzene proceeds selectively at the 2-position when MgO is used as base, even without *N*-protection (Eq. 2) [7, 8]. The strong N–Mg interaction has been proposed as the key to the effective coupling. As expected, *N*-unprotected indoles are arylated selectively at the 2-position in the presence of MgO (Eq. 3). The arylation of indolines occurs under conditions similar to those in Eq. (1) (Eq. 4) [9].

Furan [10] and its 2-formyl derivative (Eq. 5) [11] are arylated at 2- and 5-positions, respectively. Arylation of 3-ethoxycarbonylfuran and its thiophene analogue occurs selectively at the 2-position in toluene, whereas the 5-position is attacked preferentially in NMP (Eq. 6) [12]. It has been proposed that paths b and a, respectively, predominantly participate in the former and latter reactions.



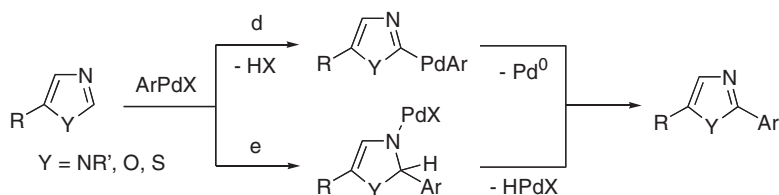
Selective 2-monoarylation of thiophene itself, and furan, can be achieved by use of excess of the substrate (Eq. 7) [10]. It has been demonstrated that use of AgF and DMSO as base and solvent, respectively, enables the reaction to proceed at 60 °C [13]. Various 2- or 3-substituted thiophenes and benzothiophenes have been subjected to catalytic arylation [2–4, 12–16]. 2,2'-Bithiophene can be diarylated at the 5,5'-positions (Eq. 8) [16]. Interestingly, *N*-phenyl-2-thiophenecarboxamides undergo 2,3,5-triarylation accompanied by a formal decarbamoylation on treatment with excess bromobenzenes (Eq. 9) [15]. The reaction involves initial coordination-assisted 3-arylation and successive decarbamoylation promoted by Pd(II) species and base in the medium. Introduction of an electron-withdrawing group to the 3-position of thiophene makes the 4-arylation possible, while reaction at the 2- and 5-positions precedes (Eq. 10) [15]. Thus, the reaction of 3-cyanothiophene affords the corresponding 2,4,5-triarylated products. Although the mechanism of the 4-arylation is not definitive, it has been proposed that the 2-arylation of 3-cyanobenzo[*b*]thiophene proceeds by path c in Scheme 1, whereas path a predominates in the reaction of 3-methoxybenzo[*b*]thiophene (Eq. 11) [4]. The polymerization of 3-alkyl-2-iodothiophenes has been reported (Eq. 12) [17].



1.4.1.2.3 Reaction of Imidazoles, Oxazoles, and Thiazoles

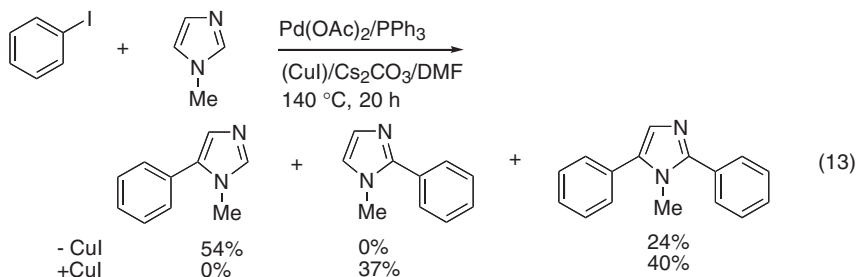
The order of reactivity for the reaction sites of azole compounds in electrophilic reactions is known to be $5 > 4 > 2$ [18]. Thus arylation at the relatively electron-rich 5-position may be regarded as similar to that of pyrroles, furans, and thiophenes (Scheme 1). In contrast, the reaction at the 2-position may be regarded as proceeding differently [3]. Although the precise mechanism is still unclear, it may involve base-assisted deprotonative palladation with the ArPd(II) species (path d in Scheme 2). Insertion of the C=N double bond into the Ar-Pd bond is also a possi-

ble pathway (path e). Anyhow, the 5-arylation usually occurs faster than the 2-arylation, although the order of reactivity can be changed by use of an additive, for example the Cu(I) species described below.



Scheme 2. Possible catalytic sequences for the Pd-catalyzed intermolecular arylation of azole compounds at the 2-position.

The reaction of 1-methyl-1*H*-imidazole with 2 equiv. iodobenzene gives its 5-phenyl derivative as the major product, with the 2,5-diphenyl derivative. Interestingly, addition of 2 equiv. CuI as promoter produces the 2-phenyl derivative together with the 2,5-diphenyl derivative; no 5-phenyl derivative is formed (Eq. 13) [3].

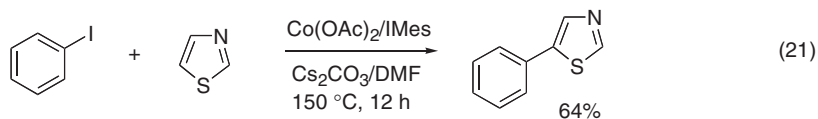
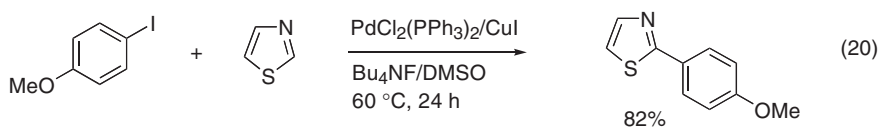
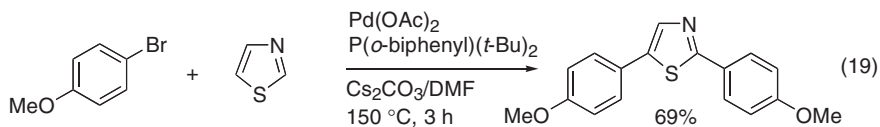
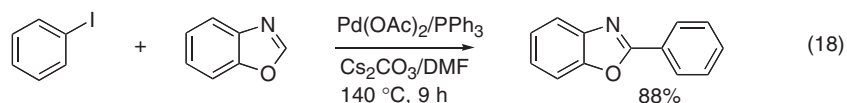
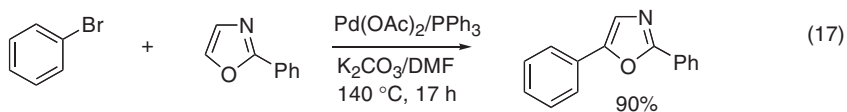
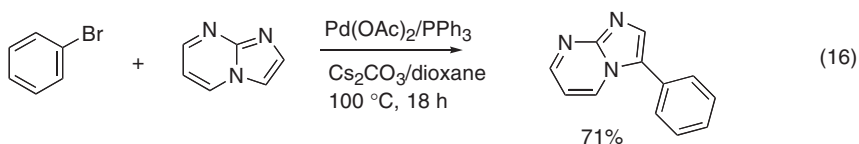
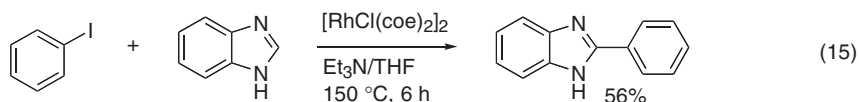
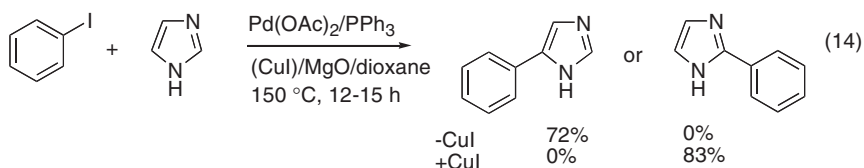


In MgO is used as base, 4(5)-phenyl- and 2-phenyl-1*H*-imidazoles can be obtained selectively by the reaction of 1*H*-imidazole itself in the absence and presence of CuI, respectively (Eq. 14) [7, 8]. The reaction of 1*H*-benzimidazole with iodobenzene also occurs at the 2-position. The same reaction can be performed by using a rhodium catalyst (Eq. 15) [19]. The arylation of imidazo[1,2-*a*]pyrimidine has also been reported (Eq. 16) [20].

Although examples for the arylation of oxazole itself are limited, reaction with 2-chloro-3,6-dialkylpyridines at the 5-position is known [6]. 2-Phenyloxazole [3] and benzoxazole [3, 10, 19, 21] are good substrates for the direct arylation (Eqs. 17 and 18) [3].

The 2,5-diarylation of thiazole can be performed effectively with a bulky phosphine ligand. In this reaction, no mono-arylated product is observed, even in the early stage of the reaction, suggesting that the second arylation proceeds relatively fast (Eq. 19) [22]. The selective 2-arylation is accomplished by using CuI and Bu₄NF as cocatalyst and base, respectively (Eq. 20) [23]. By using a catalyst system

of $\text{Co}(\text{OAc})_2\text{-IMes}$ (IMes = 1,3-bis-mesitylimidazolyl carbene) the 5-position is arylated selectively (Eq. 21) [20]. The Pd-catalyzed arylation of thiazole and 1-methylpyrrole with a polymer-linked aryl iodide has been reported [24].



Experimental

2,5-Di(*p*-anisyl)thiazole (Eq. 18)

Cs_2CO_3 (4.8 mmol, 1.56 g) was placed in a 100-mL two-necked flask and then dried at 150 °C in vacuo for 2 h. $\text{Pd}(\text{OAc})_2$ (0.1 mmol, 22.4 mg), $\text{P}(t\text{-Bu})_3$ (0.2 mmol, 40.5 mg), *p*-bromoanisole (4.8 mmol, 898 mg), thiazole (2 mmol, 170 mg), 1-methylnaphthalene (ca. 100 mg) as internal standard, and DMF (5 mL) were then added. The resulting mixture was stirred under N_2 at 150 °C for 8 h. After cooling, the reaction mixture was extracted with ethyl acetate and the extract was dried over sodium sulfate. The yield of 2,5-di(*p*-anisyl)thiazole determined by GC analysis was 76 %. Column chromatography on silica gel using hexane–ethyl acetate, 95:5, as eluent gave the product (410 mg, 69 %): m.p. 174–175 °C; ^1H NMR δ 3.84 (s, 3H), 3.86 (s, 3H), 6.93–6.97 (m, 4H), 7.51 (d, $J=8.7$ Hz, 2H), 7.85–7.90 (m, 3H); ^{13}C NMR δ 55.37, 55.40, 114.29, 114.49, 124.17, 126.73, 127.73, 127.84, 137.88, 138.22, 159.63, 161.03, 166.24; MS m/z 297 (M^+). Anal. calcd for $\text{C}_{17}\text{H}_{15}\text{NO}_2\text{S}$: C, 68.66; H, 5.08; N, 4.71; S, 10.78. Found: C, 68.47; H, 5.10; N, 4.68; S, 10.41.

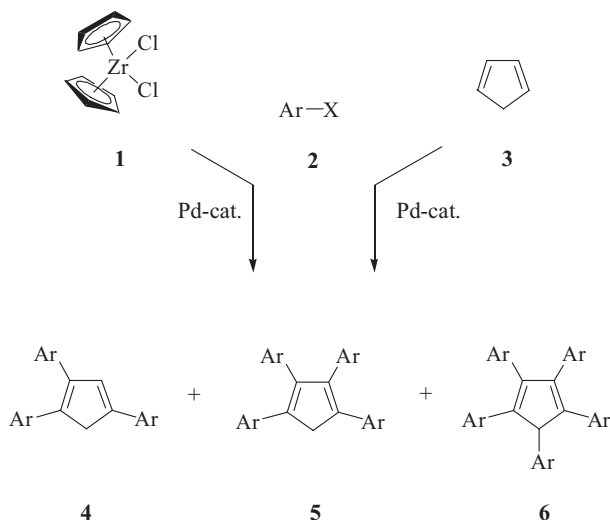
1.4.1.3 Palladium-Catalyzed Arylation of Cyclopentadienyl Compounds

Gerald Dyker

1.4.1.3.1 Introduction and Fundamental Examples

Arylated cyclopentadienes, especially pentaarylcyclopentadienes **6**, have interesting properties as ligands for transition metals [1] or as electroluminescent materials [2]. The classical methods for their preparation are multistep procedures [3], which are somewhat tedious and usually less suitable for sterically demanding aryl groups. In contrast, the palladium-catalyzed arylation of either metallocenes such as zirconocene dichloride (**1**) or simply cyclopentadiene (**3**) with aryl halides leads to the target compounds **4–6** in a single preparative step (Scheme 1) [4–6].

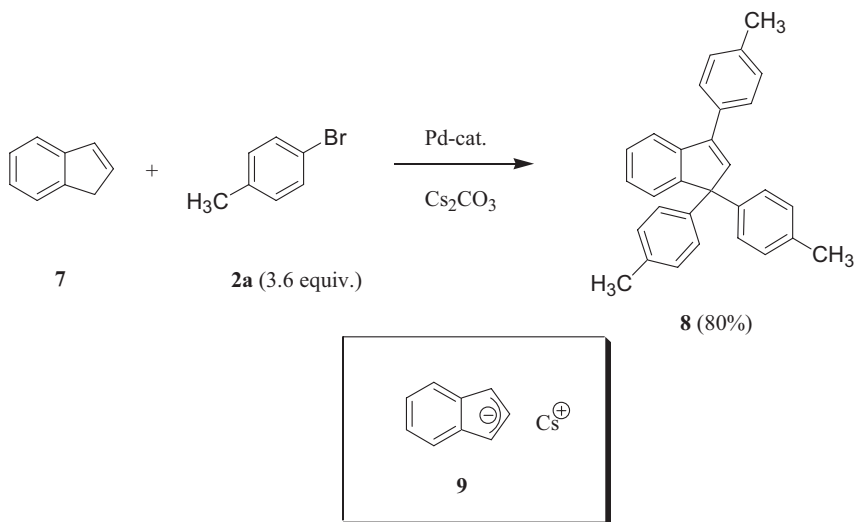
With the low-boiling cyclopentadiene (**3**) as starting material the reaction is preferably performed in a sealed tube. The product ratio of the multifold arylation, whether starting from **1** or from **3**, depends on several factors, for instance on the polarity of the solvent and on the electronic properties and bulkiness of the aryl halide **2**. Electron-withdrawing substituents on the aryl halide **2** usually somewhat favor the tetraaryl-substituted product **5**. The phosphine ligand also affects the outcome of the reaction – for arylation with meta- or para-substituted aryl halides tris(*tert*-butyl)phosphine [7] is recommended as an appropriate ligand, mainly to avoid ligand scrambling [8], which is occasionally observed with triphenylphosphine, causing minor impurities of phenyl-substituted cyclopentadienes in the crude product (so a recrystallization step is required for purification). With sterically demanding aryl halides triphenylphosphine nevertheless gives better yields than tris(*tert*-butyl)phosphine.



Scheme 1. Multiple palladium-catalyzed arylation of cyclopentadiene units; Ar = aryl, X = Br, Cl.

1.4.1.3.2 Mechanism

For the C–C bond-forming step coordination of an electrophilic aryl palladium halide to a cyclopentadienyl anion is assumed, followed by reductive elimination. Presumably the Pd catalyst is not involved in the C–H bond-breaking step, which is interpreted as an apparently simple deprotonation with cesium carbonate as base. The overall process is similar to the arylation of other soft nucleophiles [9].

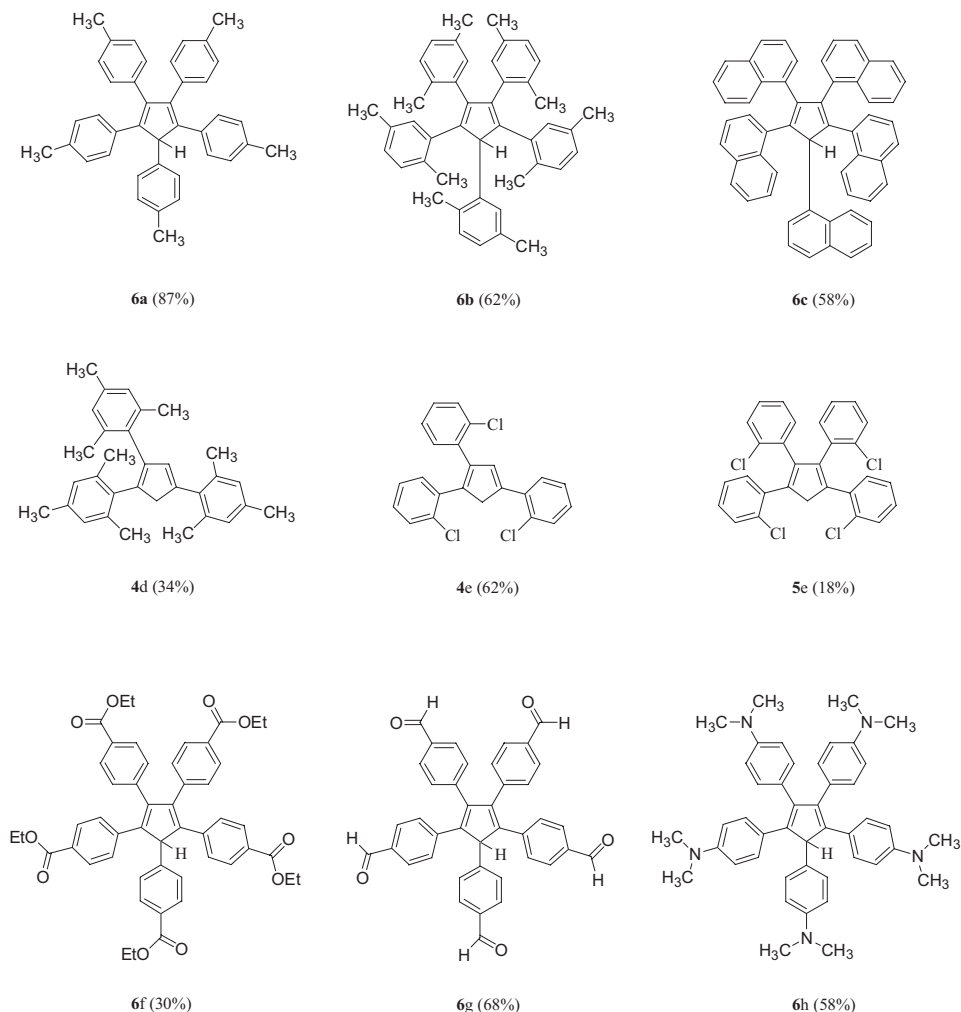


Scheme 2. Pd-catalyzed arylation of indene (**7**).

This mechanistic consideration is in accord with the result from arylation of indene (7) [5]. The arylation occurs exclusively at the 1,3-positions, those with the highest electron density, of intermediary indenyl anions (9). The related arylation of azulene also proceeds exclusively at 1,3-positions, interpreted as electrophilic aromatic substitution, again by an electrophilic aryl-Pd species [10].

1.4.1.3.3 Scope and Limitations

Simple pentaarylcyclopentadienes, for example the pentatolyl-substituted product **6a** with substituents in the para or meta position, are obtained in excellent yield. Surprisingly, rather crowded pentaarylcyclopentadienes, for example the pentaxylyl



Scheme 3. Products from the multifold arylation of cyclopentadiene.

derivative **6b** and the pentanaphthyl compound **6c**, are also accessible in good yields, as mixtures of rotamers, of course. With a combination of a bulky aryl bromide, for example *para*-xylyl bromide, and a bulky phosphine ligand, for example tris(*ortho*-tolyl)phosphine, the corresponding triarylated product **4** can be obtained selectively. The even bulkier 2,4,6-trimethylbromobenzene (**2d**) also participates in the arylation process – the three-fold product **4d** and some tetraarylated compound are isolated under these conditions.

The arylation of cyclopentadiene (**3**) with 2-chlorobromobenzene using tris(*tert*-butyl)phosphine as ligand leads to a mixture of the tetra-arylated product **5e** and its pentaarylated congener, both isolated in 17–18 % yield. With the less reactive *ortho*-dichlorobenzene the process stops at the stage of the triarylated species **4e**, which can then be further arylated with 2-chlorobromobenzene.

Both, esters and tertiary amino groups are tolerated, giving rise to products **6f** and **6h** which are useful as centers for dendrimeric structures. The pentakisaldehyde **6g** was obtained from 4-bromobenzaldehyde protected as the ethylene glycol acetal. Attempts to use heterocyclic bromides for arylation were hitherto unsuccessful.

Experimental

1,2,3,4,5-Pentakis(2,5-dimethylphenyl)cyclopenta-1,3-diene (**6b**)

A mixture of 66 mg (1.0 mmol) cyclopentadiene (**3**), 1.11 g (6.00 mmol) 1-bromo-2,5-dimethylbenzene, 1.96 g (6.00 mmol) cesium carbonate, 22.4 mg (50 μ mol) palladium acetate, 10 mL dimethylformamide, and 52 mg (200 μ mol) triphenylphosphine was heated under argon in a screw-capped tube for 23 h at 140 °C. After cooling to room temperature 50 mL CH₂Cl₂ and 12 mmol *para*-toluene sulfonic acid were added, with stirring, and after 10 min the mixture was filtered through 5 g silica with 25 mL of CH₂Cl₂ as eluent. The solvent was evaporated at 50 °C/15 mbar. The residue was dried in vacuo at 120 °C/0.5 mbar and finally fractionated by flash chromatography on silica gel (petroleum ether–ethyl acetate, 50:1; *R*_f = 0.30, 0.14, 0.03, 0.00). The fraction with *R*_f = 0.14 is collected, giving 174 mg (62 %) of slightly colored **6b** as a mixture of rotamers with m.p. 194–196 °C; ¹H NMR: δ = 1.72–2.46 (m, 30H), 4.86–5.45 (m, 1H; actually singlets at 4.86, 5.07, 5.10, 5.25, 5.29, and 5.45), 6.46–7.10 (m, 15H); MS *m/z* = 586 (*M*⁺).

1.4.2

Palladium-catalyzed Arylation Reactions via Palladacycles

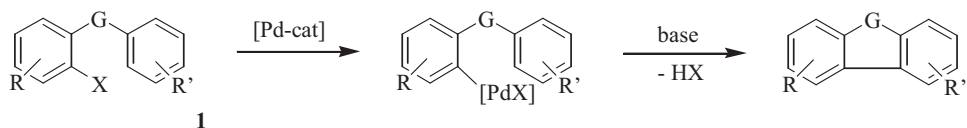
1.4.2.1 Intramolecular Biaryl Bond Formation – Exemplified by the Synthesis of Carbazoles

Robin B. Bedford, Michael Betham, and Catherine S. J. Cazin

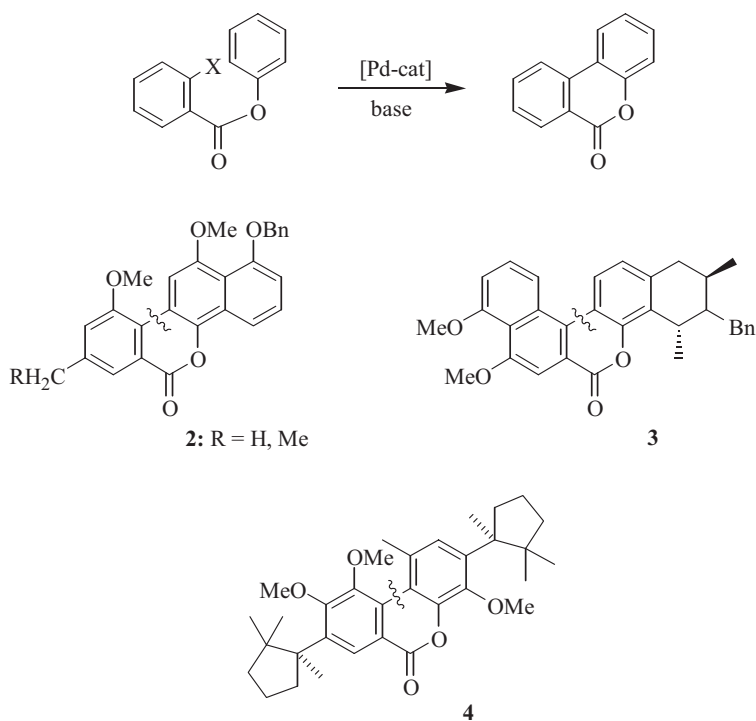
1.4.2.1.1 Introduction and Fundamental Examples

Palladium catalyzed C–H activation is a powerful tool for synthesis of biaryls from “tethered” aryl halide and triflate substrates of type **1** (Scheme 1). This technique

has proved useful in the synthesis of six-membered heterocycles [1] such as quinolinones [2, 3], pyrans, thiazine dioxides, and pyranones [2]. Scheme 2 outlines the synthesis of the pyranone structure with selected illustrative examples. These are the benzylated forms of defucogilocarcins M and E, **2** [4], and compounds **3** and **4**, intermediates in syntheses of dioncophylline A and mastigophorene B respectively [5, 6].



Scheme 1. Intramolecular biaryl bond formation.



Scheme 2. Intramolecular biaryl bond formation in the synthesis of pyranones and illustrative examples (the new bonds formed are indicated).

Five-membered rings are also readily synthesized using this coupling methodology, enabling the production of dibenzo[*b,d*]fused heterocycles such as dibenzofurans [2, 7], carbazoles [7, 8] (Scheme 1, G = O, NR respectively), and related compounds [8, 9]. Carbazoles are important structural motifs found in pharmaceuti-

cals, natural products, agrochemicals, and dyes [10, 11]. For example, carvedilol, (Fig. 1) is a beta-blocker used in the treatment of hypertension and angina and carazostatin is one of a family of carbazoles produced by bacteria that are potent free-radical scavengers and act as anti-oxidants. Ellipticine and its derivatives, in particular 9-hydroxyellipticine, have potent anti-tumor activity.

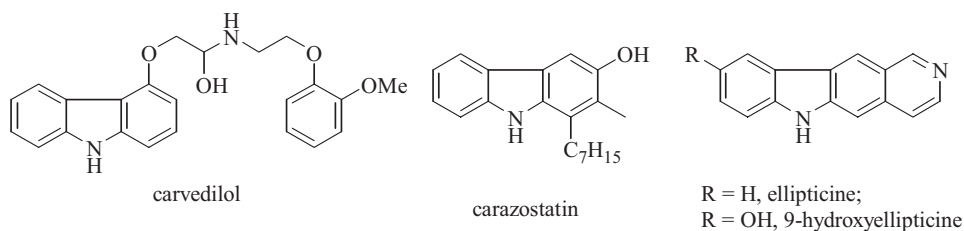
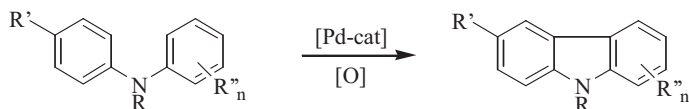


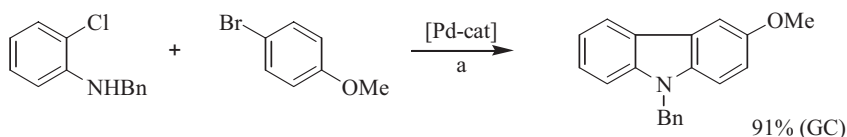
Figure 1. Examples of biologically active carbazoles.

C–H activation can be used to generate carbazoles from *N*-aryl anilines by palladium catalyzed oxidative coupling (Scheme 3) [12]. Although this is a powerful method, it is ultimately limited by the fact that more heavily substituted *N*-aryl anilines may not couple selectively, leading to the formation of more than one product.



Scheme 3. Formation of carbazoles via palladium catalyzed oxidative coupling.

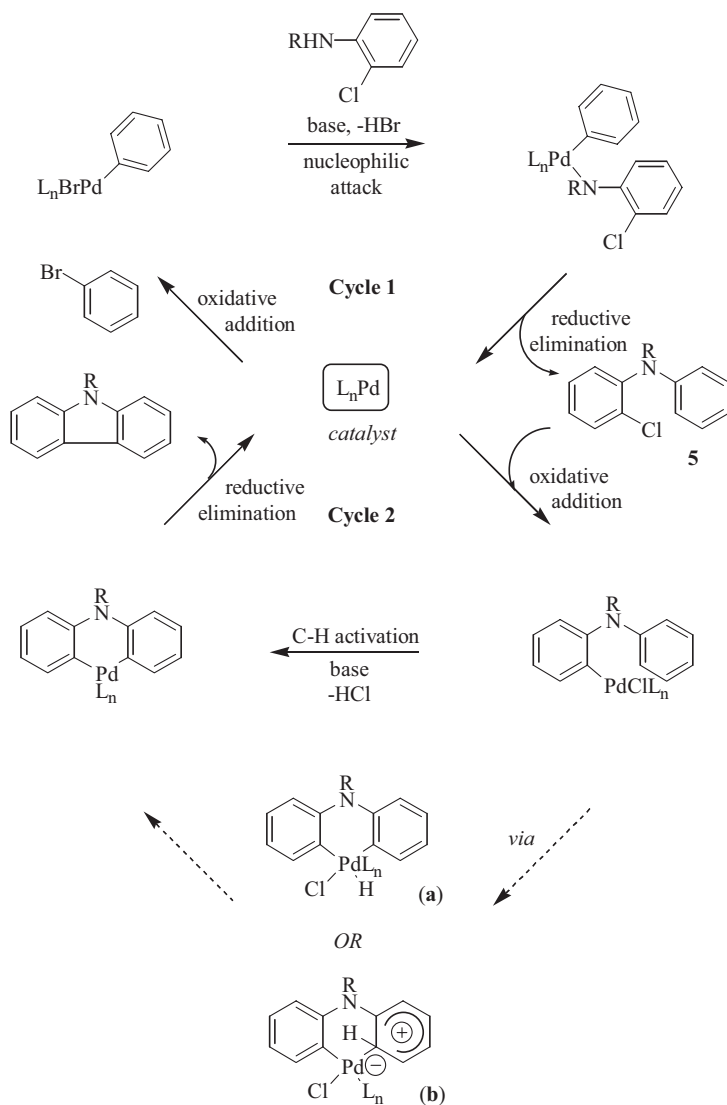
The dehydrohalogenation approach outlined in Scheme 1 reduces problems of selectivity in the synthesis of carbazoles. The method can be improved further by producing the *N*-aryl-2-haloaniline starting materials in the same pot as the subsequent carbazole product. This is achieved by Buchwald–Hartwig amination of 2-chloroanilines with aryl bromides [13]. An illustrative example of this one-pot procedure is shown in Scheme 4.



Scheme 4. One-pot synthesis of a carbazole via consecutive Buchwald–Hartwig amination and ring-closing reactions:
(a) Pd(OAc)₂ (5 mol%), P^tBu₃ (7 mol%), NaO^tBu, toluene, reflux, 24h.

1.4.2.1.2 Mechanism

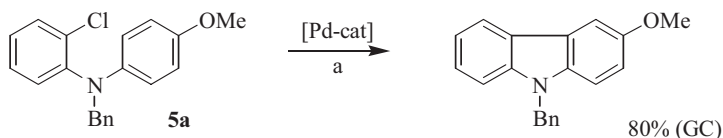
A plausible mechanism for the one-pot synthesis of carbazoles is shown in Scheme 5. It consists of two interlinked catalytic cycles. In the first cycle a classical Buchwald–Hartwig amination reaction occurs to generate an intermediate **5** which then enters the second cycle by oxidative addition to Pd(0). The resulting Pd(II) complex then undergoes intramolecular C–H activation to give a six-membered palladacycle which subsequently yields the carbazole by reductive elimination.



Scheme 5. Possible mechanism for the synthesis of carbazoles from 2-chloroanilines and aryl bromides (ring substituents omitted for clarity).

The C–H activation step could, in principle, occur either by oxidative addition of the C–H bond – pathway (a) – or by electrophilic displacement – pathway (b). The oxidative addition pathway would proceed via the formation of a palladium(IV) species. Although such intermediates have been postulated in some coupling reactions catalyzed by palladacycles, as yet no conclusive experimental evidence has been presented [14]. It is perhaps more likely that C–H activation results from electrophilic displacement of the ortho proton [15].

To confirm that the compounds **5** are indeed the intermediates that enter the second coupling step, a representative example, **5a**, was subjected to the standard reaction conditions and shown to generate the desired carbazole in good yield (Scheme 6).

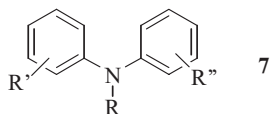


Scheme 6. Ring closing reaction of a pre-formed intermediate: (a) $\text{Pd}(\text{OAc})_2$ (5 mol%), P^tBu_3 (7 mol%), NaO^tBu , toluene, reflux, 24 h.

1.4.2.1.3 Scope and Limitations

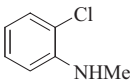
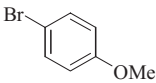
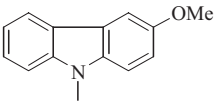
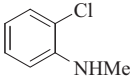
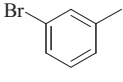
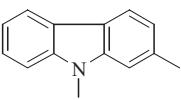
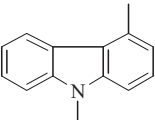
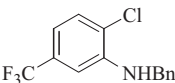
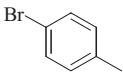
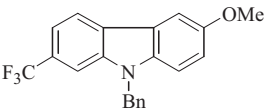
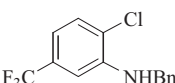
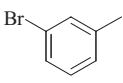
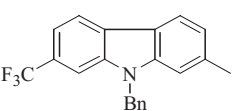
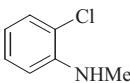

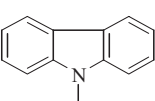
Examples of the one-pot method are given in Table 1 [13]. The coupling works not only with aryl bromides that are electronically non-activated with regard to oxidative addition, for example bromobenzene and 3-bromotoluene, but also for the deactivated substrate 4-bromoanisole. When 3-bromotoluene is used as the substrate, in principle, two isomers can form. This indeed occurs and both the 2- and 4-methyl isomers are produced in a 5:1 ratio. In contrast, when *N*-benzyl-2-chloro-5-trifluoromethylaniline, **6**, is used as substrate there is no evidence for formation of the second isomer.

In all successful double coupling reactions small amounts of the hydrodehalogenated products **7** ($\text{R} = \text{Me}$, Bn) are seen and in all the reactions, except with **6**, small amounts of the intermediates **5** are also observed. The lack of any intermediates **5** when **6** is used as a substrate is presumably because the CF_3 group activates the chloride for oxidative addition.



Because 2-haloanilines are strongly electronically deactivated with regard to oxidative addition, it may be expected that there is sufficient disparity in reactivity between *N*-benzyl-2-chloroaniline and 4-chloroanisole for them to undergo the sequential coupling reaction. Very little carbazole product is formed, however, the major product being the intermediate **5a**. In this case it seems that the rate of the

Table 1. Examples of the one-pot, double-coupling method.
 Conditions: Pd(OAc)₂ (4–5 mol%), P^tBu₃ (5–7 mol%), NaO^tBu,
 toluene, reflux, 24h.

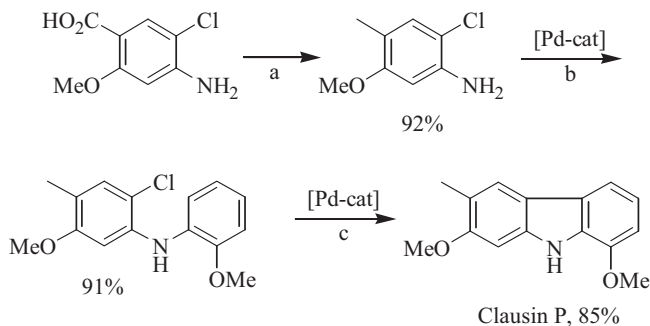
Starting materials		Products	Isolated yield ^a (GC yield)
			47(73)
			57(75)
			(~15)
			27(50)
			51(69)
			61(85)

^a Non-optimized yields.

amination is too slow for substantial product formation and conversion of the intermediate **5a** to the product is probably limited by catalyst longevity. The coupling of benzyl-2-bromoaniline and 4-bromoanisole also fails. In this case little of the intermediate is formed, indicating that the problem lies in the amination step. This may be a result of steric hindrance by the bromide in the 2-position of the aniline.

In contrast, with the *N*-alkylated 2-chloroanilines, simple unsubstituted 2-chloroanilines give no or, under substantially more forcing conditions (10 mol% catalyst, 60 h), trace amounts of the desired carbazoles. In these reactions the main products are the intermediates **5** (R = H) [13]. To circumvent this problem it is necessary to split the double-coupling into its constituent steps [16]. Optimization studies show that the amination proceeds when the solvent is toluene but not 1,4-dioxane, whereas ring-closure is facile in dioxane but does not work in toluene.

Splitting of the steps enables facile, compact synthesis of the previously unsynthesized natural carbazole alkaloid, Clausine P (Scheme 7) [16, 17].



Scheme 7. Synthesis of Clausine P. (a) $BH_3 \cdot SMe_2$, C_6H_5Cl , $0^\circ C$ for 15 min then $115^\circ C$ for 18 h. (b) $Pd(OAc)_2$ (4 mol%), P^tBu_3 (5 mol%), NaO^tBu , toluene, reflux, 18 h (high yield, not purified) (c) $Pd(OAc)_2$ (4 mol%), P^tBu_3 (5 mol%), NaO^tBu , 1,4-dioxane, reflux, 18 h.

A large drawback of this “double-coupling” method is the need to handle and use the highly air-sensitive, low-melting tri-*tert*-butylphosphine as the ligand [13]. Fu and co-workers demonstrated that the phosphonium salt $[HP^tBu_3][BF_4]$ can be used as a solid, air-stable replacement for P^tBu_3 in a range of coupling reactions [18]. The ligand is generated in situ by deprotonation with the base required in the coupling reaction. The same is found to be true here, with the phosphonium salt giving equal or better results than the free phosphine.

Experimental

9-Benzyl-3-methoxycarbazole

A mixture of 4-bromoanisole (0.225 g, 1.22 mmol), *N*-benzyl-2-chloroaniline (0.283 g, 1.30 mmol), sodium *t*-butoxide (0.586 g, 6.10 mmol), palladium acetate (0.0137 g, 0.061 mmol), tri-*t*-butylphosphine (0.0173 g, 0.086 mmol) in toluene (13 mL) was heated at reflux temperature for 24 h. The reaction was quenched with a solution of hydrochloric acid (3.5 M, 10 mL) and toluene (30 mL) was added. The phases were separated and the aqueous phase was extracted with toluene (1 \times 30 mL), dichloromethane (4 \times 30 mL) and toluene (1 \times 30 mL). The organic extracts were combined, dried over magnesium sulfate, filtered through Celite, and the solvents were removed on a rotary evaporator. The product was purified by flash chromatography (SiO_2 , petroleum ether–EtOAc, 9:1, R_F = 0.3) to give a pale yellow solid in 40 % yield (non-optimized, GC analysis of the reaction shows 91 % conversion to the carbazole). 1H -NMR (300 MHz, $CDCl_3$, 298 K): δ 3.96 (s, 3H, OCH_3), 5.52 (s, 2H, CH_2), 7.10 (dd, $^4J(H^2H^4)$ = 2.5 Hz, $^3J(H^2H^1)$ = 8.8 Hz, 1H, $Ar-H^2$), 7.15 (m, 2H, $Ar-H$), 7.21–7.34 (m, 5H, $Ar-H^1$, $Ar-H^6$ and 3 \times $Ar-H$), 7.37 (br d, $^3J(H^8H^7)$ = 8.2 Hz, 1H, $Ar-H^8$), 7.45 (ddd, $^4J(H^7H^5)$ = 1.1 Hz, $^3J(H^7H^8)$ = 8.2 Hz,

$^3J(\text{H}^7\text{H}^6) = 7.0$ Hz, 1H, Ar- H^7), 7.65 (d, $^4J(\text{H}^4\text{H}^2) = 2.5$ Hz, 1H, Ar- H^4), 8.12 (ddd, $J = 0.6$ Hz, $^4J(\text{H}^5\text{H}^7) = 1.1$ Hz, $^3J(\text{H}^5\text{H}^6) = 7.9$ Hz, 1H, Ar- H^5). $^{13}\text{C}\{-^1\text{H}\}$ -NMR (300 MHz, CDCl_3 , 298 K): δ 46.5 (s, CH_2), 56.0 (s, CH_3), 103.3 (s, CH, C^4), 108.9 (s, CH, C^8), 109.6 (s, CH), 114.8 (s, CH, C^2), 118.7 (s, CH), 120.3 (s, CH, C^5), 122.7 (s, C), 123.3 (s, C), 125.8 (s, CH, C^7), 126.3 (s, CH), 127.3 (s, CH), 128.7 (s, CH), 135.6 (s, C), 137.3 (s, C), 141.1 (s, C), 153.7 (s, C). HRMS (CI) $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{20}\text{H}_{17}\text{NO}$: 288.1388. Found: 288.1386. Anal. Calcd for $\text{C}_{20}\text{H}_{17}\text{NO}$: C, 83.6 %; H, 6.0 %; N, 4.9 %. Found: C, 82.2 %; H, 5.9 %; N, 4.65 %.

Clausine P

2-Chloro-5-methoxy-*N*-(2-methoxyphenyl)-4-methylaniline (1.12 g, 4.0 mmol) was dissolved in 1,4-dioxane (3 mL) and sodium *tert*-butoxide (1.93 g, 20 mmol) was added. Palladium acetate (0.036 g, 0.16 mmol) and tri-*t*-butylphosphine (0.041 g, 0.20 mmol) were dissolved in dioxane (3 mL) and added to the reaction mixture. Finally, dioxane (10 mL) was added and the reaction was heated at reflux for 18 h. The reaction was quenched by addition of hydrochloric acid (2 M, 5 mL). The product was extracted with dichloromethane (3×50 mL), the extract was dried over magnesium sulfate and filtered, and the solvent was removed under reduced pressure to give a thick brown oil. The crude product was purified by column chromatography (SiO_2 , petroleum ether–EtOAc, 5:1, $R_F = 0.2$) to give Clausine P as a yellow solid (0.82 g, 85 %). ^1H NMR (300 MHz, CDCl_3 , 298 K): δ 1.57 (br. s, 2H, H_2O), 2.29 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 6.75 (d, $^3J(\text{H}^2\text{H}^3) = 7.8$ Hz, 1H, Ar- H^2), 6.81 (s, 1H, Ar- H^8), 7.04 (dd, $^3J(\text{H}^3\text{H}^4) = 7.8$ Hz, $^3J(\text{H}^3\text{H}^2) = 7.8$ Hz, 1H, Ar- H^3), 7.49 (d, $^3J(\text{H}^4\text{H}^3) = 7.8$ Hz, 1H, Ar- H^4), 7.69 (s, 1H, Ar- H^5), 8.04 (br. s, 1H, NH). $^{13}\text{C}\{-^1\text{H}\}$ -NMR (300 MHz, CDCl_3 , 298 K): δ 17.2 (s, Ar- CH_3), 55.9 (s, 2 x OCH_3), 93.0 (s, CH, C^8), 105.0 (s, CH, C^5), 112.5 (s, CH, C^2), 117.0 (s, C^6), 119.7 (s, C), 120.0 (s, CH, C^3), 122.0 (s, CH, C^4), 125.0 (s, C), 129.7 (s, C), 139.3 (s, C), 145.9 (s, C^1), 157.8 (s, C^7). HRMS (CI) $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{15}\text{H}_{15}\text{NO}_2$: 241.1103. Found 241.1144. Anal. Calcd for $\text{C}_{15}\text{H}_{15}\text{NO}_2 \cdot \text{H}_2\text{O}$: C, 74.7 %; H, 6.3 %; N, 5.8 %. Found C, 73.8 %; H, 6.2 %; N, 5.5 %.

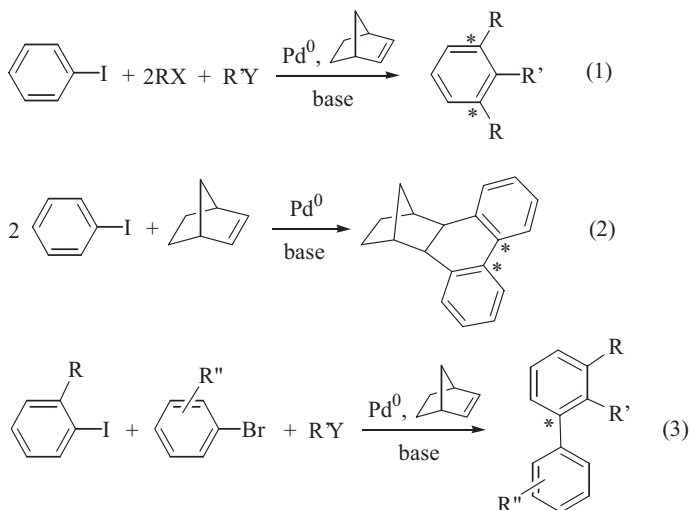
1.4.2.2 Carbopalladation–Cyclopalladation Sequences

Marta Catellani and Elena Motti

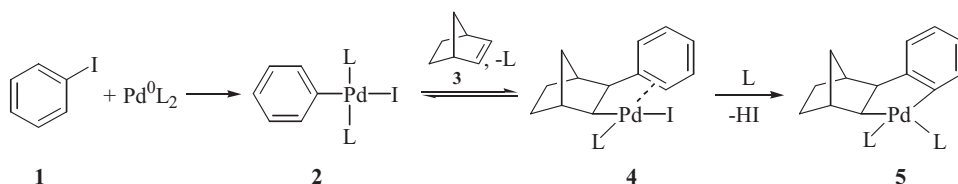
1.4.2.2.1 Introduction

We report an $\text{sp}^2\text{-C-H}$ transformation method based on reactions involving palladacycles. General Eqs (1)–(3) represent the processes described; RX is an alkyl halide and R'Y is an olefin, a terminal alkyne or an arylboronic acid ($\text{Y} = \text{H}$ or $\text{B}(\text{OH})_2$). Asterisks mark the transformed C atoms.

C–H transformation is achieved by cyclometallation by use of a unique catalytic system which involves the in-situ formation of a palladacycle [1]. Our work in this field takes advantage of the stability toward β -hydrogen elimination of *cis,exo*-aryl-norbornylpalladium complexes formed by a sequence of oxidative addition of an aryl halide to palladium(0) and stereoselective insertion of norbornene into the



resulting arylpalladium bond (Scheme 1). Because of the C–H and C–Pd bond anti configuration these species do not readily undergo β -H elimination but, being rather reactive, are subject to a great variety of transformations. In the presence of a base such as potassium carbonate they readily give palladacycles by activation of a usually inert aromatic C–H bond. The cyclopalladation reaction, which is likely facilitated by coordination of the aromatic ring with palladium, occurs under mild conditions and proceeds through an electrophilic aromatic substitution. In fact the reaction is favored by electron-donating substituents in the aromatic ring of complex 4, as shown for following the cyclization process by NMR spectroscopy.

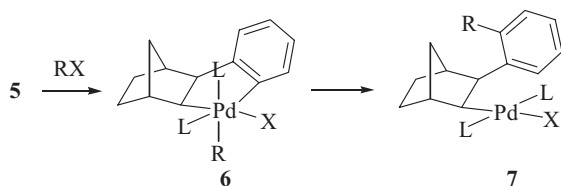


Scheme 1. Palladacycle formation through a sequence of oxidative addition, insertion, and electrophilic aromatic substitution. L = phosphorous or nitrogen ligands, solvent, or coordinating species.

1.4.2.2.2 Palladacycle Reactivity

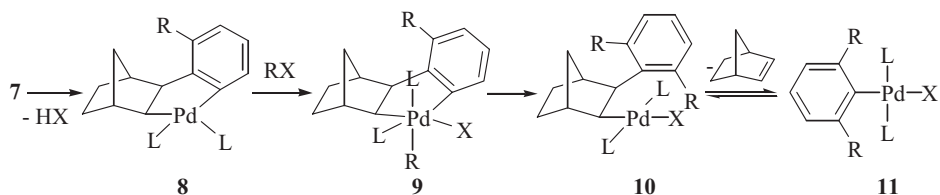
Palladacycle 5 reacts in various ways depending on ligands and reaction conditions. In particular it readily undergoes oxidative addition of alkyl halides to form a palladium(IV) complex 6, which has been isolated and characterized with stabilizing nitrogen ligands such as phenanthroline. This palladium(IV) metallacycle

has a strong tendency to reductively eliminate to palladium(II) by selective alkyl–aryl coupling, giving species **7** (Scheme 2).



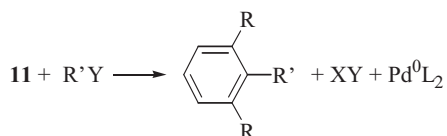
Scheme 2. Palladium(IV) metallacycle formation and subsequent reductive elimination. Isolated species with L–L = phen; R = Me, CH₂=CHCH₂, 4-NO₂C₆H₄; X = Br, Cl.

At this point the situation becomes analogous to that enabling the formation of palladacycle **5** from **4** and so a new *o*-substituted palladacycle **8** forms as a result of a second intramolecular C–H activation. Complex **8** again undergoes RX oxidative addition to afford the new palladium(IV) metallacycle **9** which reductively eliminates by selective migration of the R group on to the aromatic site of the same palladacycle to give the palladium(II) species **10**, a disubstituted homologue of complex **7** (Scheme 3).



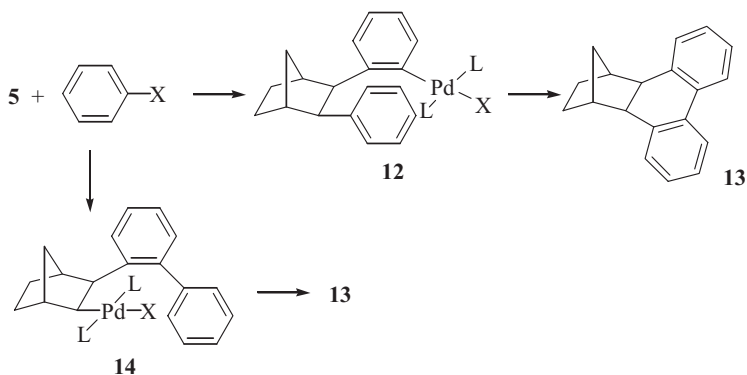
Scheme 3. Intramolecular C–H activation toward mono- and di-*o*-alkylation of palladacycles and norbornene deinsertion process.

The resulting complex **10** can be viewed as the product of an insertion equilibrium analogous to that leading from **2** to **4** (Scheme 1). This time, however, the presence of the two ortho substituents shifts the equilibrium to the left and norbornene is expelled with formation of the *o*-dialkylated arylpalladium halide species **11**. This lends itself to a variety of reactions enabling the formation of organic products and palladium(0), which can be represented schematically as follows (Scheme 4).



Scheme 4. Termination process regenerating palladium(0).

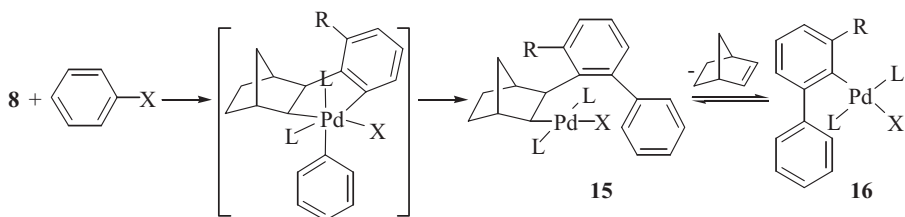
Complex **5** (Scheme 1) follows a different pathway in reactions with aryl halides ($R = \text{aryl}$ in RX). This time the aryl group reacts preferentially with the norbornyl site of the palladacycle rather than with the aryl site (probably via a palladium(IV) metallacycle of type **6**). As a consequence, norbornene is no longer expelled and is incorporated into a condensed ring instead. The minor aryl portion that migrates on to the aryl site (complex **14**) also retains norbornene and gives the same product **13**. A C–H transformation process is thus operating in ring formation from **12** or **14** to **13** (Scheme 5) [2].



Scheme 5. Reaction pathways for ring closure on aromatic sites.

A recent advance on the method outlined above (Eq. (3), schemes 1–5), is based on the discovery of the *ortho* effect – when the palladacycle contains an *ortho* substituent, as in **8**, arylation occurs entirely at the aryl and not at the norbornyl site [3]. This is probably because of the steric effect of the *ortho* substituent which renders attack at the aryl site much more favorable by preferentially weakening the palladium–carbon bond of the precursor of **15** (Scheme 6).

The consequence is the formation of a sterically hindered complex which readily expels norbornene thus giving rise to the biphenyl complex **16**. The latter can be caused to react according to Eq. (3).

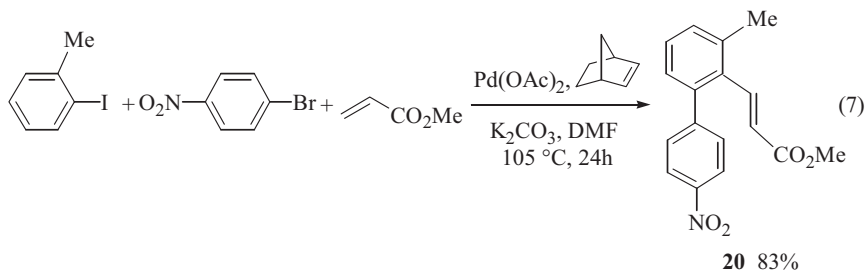
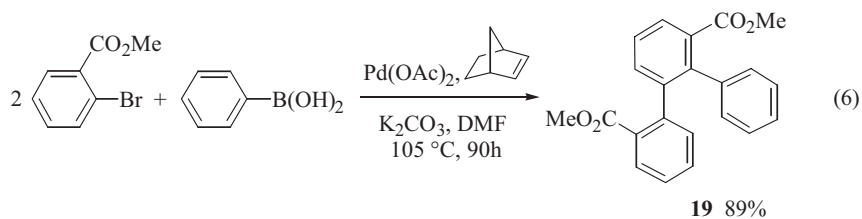
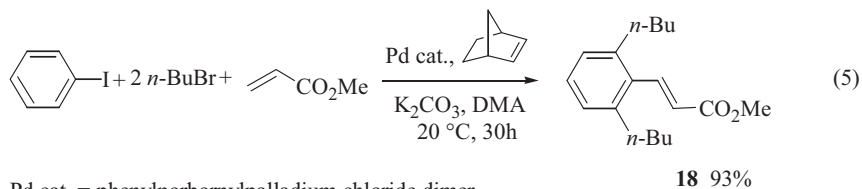
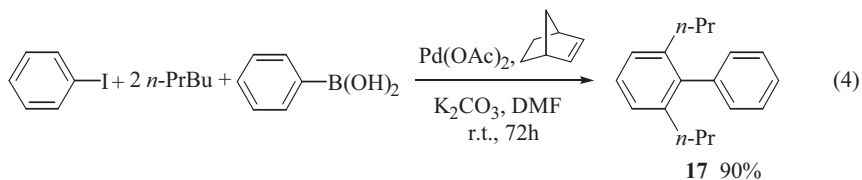


Scheme 6. The *ortho* effect leading to aromatic arylation.

1.4.2.2.3 Scope and Limitations

The C–H transformations reported here are tolerant of a variety of functional groups but rather sensitive to *ortho* substituents which strongly interact with pal-

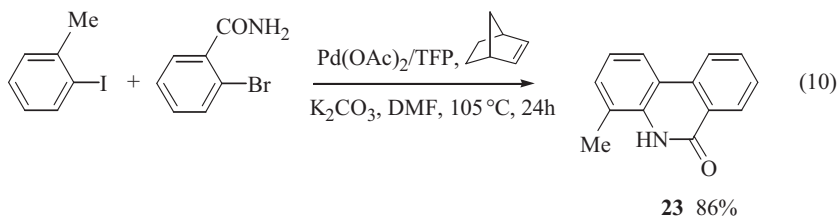
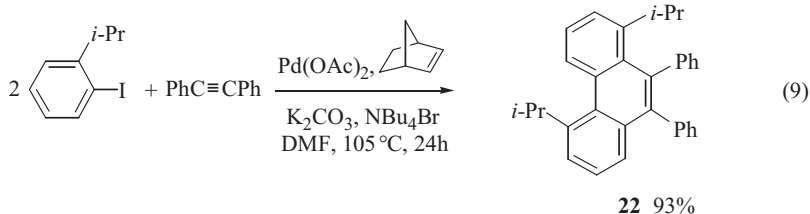
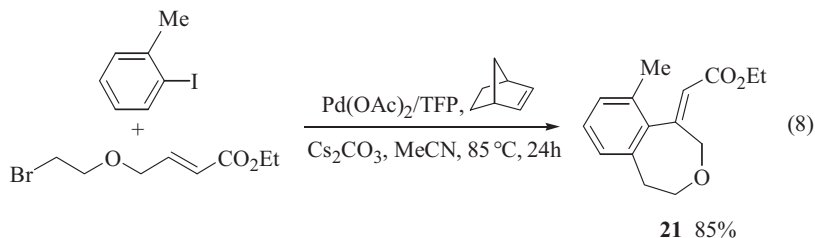
ladium or exert significant steric hindrance. The following examples illustrate some specific cases covered by general Eqs (1) and (3).



Eqs (4)–(7) show examples of classes of compounds which have been obtained by transformation of one or two $\text{sp}^2\text{C-H}$ bonds in the presence of a catalytic system resulting from the cooperation of organic (norbornene) and inorganic (palladium) species. In particular the first example (Eq. 4) entails di-*n*-propylation of the two ortho positions of the phenyl ring of iodobenzene followed by coupling with phenylboronic acid to give 2,6-di-*n*-propyl-1,1'-biphenyl [4]. The second example (Eq. 5) shows the di-*n*-butylation of the same ortho positions, this time followed by a Heck-type reaction with methyl acrylate, leading to 2,6-di-*n*-butyl cinnamic acid methyl ester [5]. The third case (Eq. 6) takes advantage of the ortho effect to form a palladium-bonded biphenyl species which readily couples with the phenyl group

of phenylboronic acid to give a diacid derivative of 2-terphenyl (2,3'-dimethoxycarbonyl-1,1';2',1''-terphenyl) [6]. In the last example (Eq. 7) the palladium-bonded biphenyl group, formed by coupling of two differently substituted aryl moieties, inserts a terminal olefin to form 2-(4-nitrophenyl)-6-methyl cinnamic acid methyl ester [7].

Further extension of the methods shown above has led to new reactions involving condensed ring formation as reported in Eqs (8)–(10).



The synthesis of selectively substituted benzoxepines from *ortho*-substituted aryl iodides and bromoenates has been achieved by Lautens and coworkers by palladacycle alkylation followed by an intramolecular Heck reaction under the modified conditions reported in Eq. (8) for synthesis of 1-(1-ethoxycarbonylmethylene)-9-methyl-4,5-dihydro-3-benzoxepine [8]. In the second example (Eq. 9) the palladium-bonded biphenyl inserts diphenylacetylene to form 1,5-di-*i*-propyl-9,10-diphenylphenanthrene [9]. In the last case the synthesis of 4-methyl-5H-phenanthridin-6-one is achieved by palladium-catalyzed sequential C–C and C–N bond formation starting from *o*-iodotoluene and *o*-bromobenzamide [10].

Experimental

2,6-Di-*n*-propyl-1,1'-biphenyl (17) [4]

A mixture of $\text{Pd}(\text{OAc})_2$ (9.0 mg, 0.04 mmol), K_2CO_3 (332 mg, 2.4 mmol), *o*-iodobenzene (82 mg, 0.4 mmol), *n*-propyl bromide (220 mg, 1.6 mmol), norbornene (38 mg, 0.4 mmol), and phenylboronic acid (59 mg, 0.48 mmol) in dimethylformamide (DMF, 5 mL) was stirred at r.t. under nitrogen for 72 h in a Schlenk-type flask. The mixture was diluted with CH_2Cl_2 (15 mL) and extracted with 5 % H_2SO_4 (2×15 mL). The organic phase was dried over Na_2SO_4 . After removal of the solvent under reduced pressure compound **17** was isolated as a colorless oil (86 mg, 90 % yield) by flash chromatography on silica gel using hexane as eluent ($R_F = 0.4$). ^1H NMR (CDCl_3 , 300 MHz): $\delta = 0.75$ (t, $J = 7.3$ Hz, 6H, 2CH_3), 1.41 (m, 4H, $2\text{CH}_2\text{CH}_3$), 2.27 (m, 4H, $2\text{CH}_2\text{Ar}$), 7.15 (m, 2H, H_2' , H_6'), 7.23, 7.11 (AB_2 system, $J = 7.3$ Hz, 3H, H_4 , H_3 , H_5), 7.33 (m, 1H, H_4'), 7.40 (m, 2H, H_3' , H_5').

E-3-[6'-Methyl-2'-(4"-nitrophenyl)phenyl]propenoic Acid Methyl Ester (21) [7]

A mixture of $\text{Pd}(\text{OAc})_2$ (2.5 mg, 0.011 mmol), K_2CO_3 (185 mg, 1.34 mmol), *o*-iodotoluene (122 mg, 0.56 mmol), *p*-nitrobromobenzene (114 mg, 0.56 mmol), norbornene (53 mg, 0.56 mmol), and methyl acrylate (78 mg, 0.90 mmol) in DMF (5 mL) was stirred at 105 °C under nitrogen for 24 h in a Schlenk-type flask. After cooling to r.t. the mixture was diluted with dichloromethane (CH_2Cl_2 , 30 mL) and extracted with 5 % H_2SO_4 (2×15 mL). The organic phase was washed with water (20 mL) and dried over Na_2SO_4 . After removal of the solvent under reduced pressure compound **21** was isolated as a pale yellow solid (138 mg, 83 % yield), m.p. (hexane) 98–99 °C by flash chromatography on silica gel using a mixture of hexane–ethyl acetate, 95:5, as eluent ($R_F = 0.1$). ^1H NMR (CDCl_3 , 300 MHz): $\delta = 2.45$ (s, 3H, CH_3), 3.71 (s, 3H, CO_2CH_3), 5.75 (d, $J = 16.3$ Hz, 1H, C2), 7.17 (dd, $J = 6.5$, 2.5 Hz, 1H, H_3'), 7.37–7.28 (m, 1H, H_4' , H_5'), 7.48–7.42 (m, 2H, H_2'' , H_6''), 7.67 (d, $J = 16.4$ Hz, 1H, C3), 8.26–8.21 (m, 2H, H_3'' , H_5''). IR (KBr, cm^{-1}): ν 1718, 1642.

1.4.3

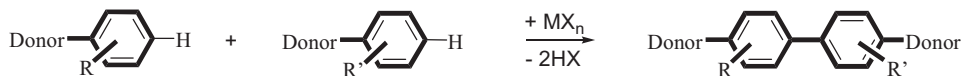
Oxidative Arylation Reactions

Siegfried R. Waldvogel and Daniela Mirk

1.4.3.1 Introduction and Fundamental Examples

On oxidation, electron-rich aryls can undergo oxidative coupling reactions forming aryl–aryl bonds. The dehydrodimerization is a twofold C–H transformation which can proceed by several reaction pathways depending on the nature of the substrate and reagent mixture. Structural requirements include electron-rich arene moieties that incorporate activating substituents. Common donor functionalities are alkyl, alkoxy, amino, and hydroxy groups. If the donor has an acidic proton, e.g. phenols or primary anilines, the oxidative transformation is named a phenol-coupling reaction. Usually, the newly formed bond is ortho to the donor func-

tions, because of the templating effect with the reagent. O-Protected phenols follow a different reaction mechanism and result preferentially in the biaryl coupled para to the donor substituents. When the transformation outlined in Scheme 1 is performed intermolecularly, the well established homo coupling ($R = R'$) occurs, whereas few examples of the oxidative cross-coupling reaction ($R \neq R'$) are known. In contrast, intramolecular oxidative cyclization can be efficiently achieved when the coupling partners are sufficiently electron rich. Otherwise, dimer formation is observed. The moieties involved in this particular transformation require activation of at least some alkyl substituents on the arene.

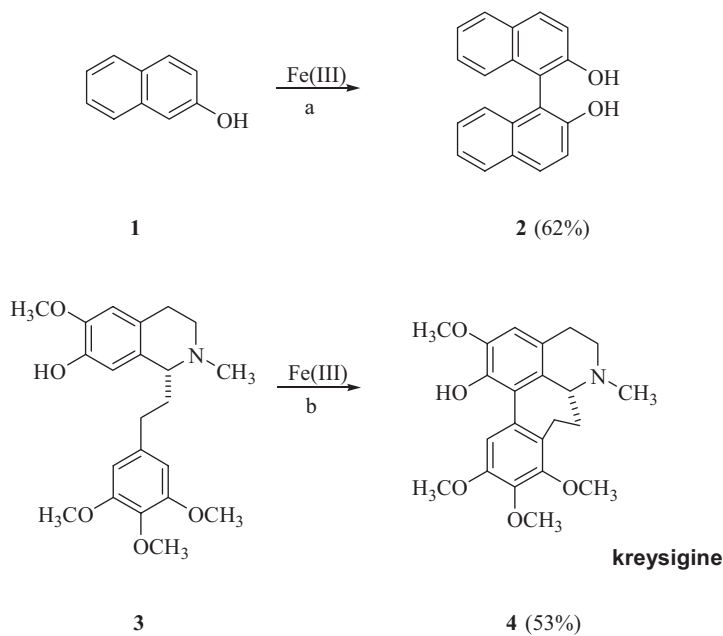
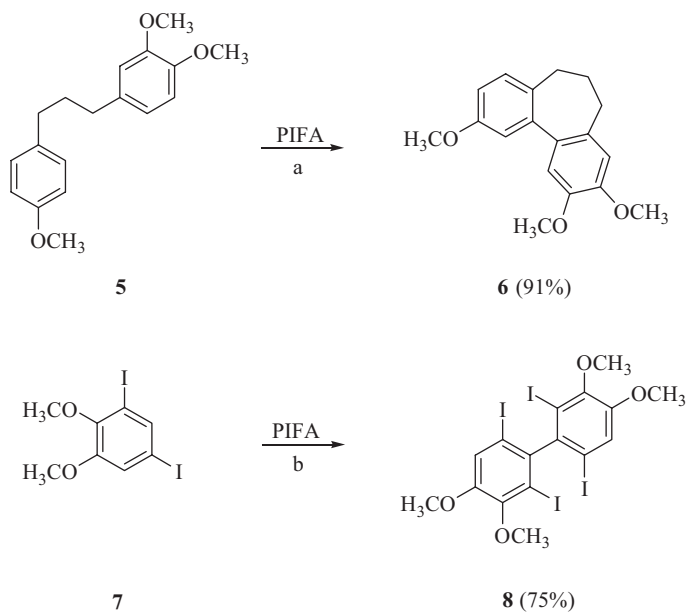


Scheme 1. Dehydrodimerization of electron-rich aryls (general pictogram).

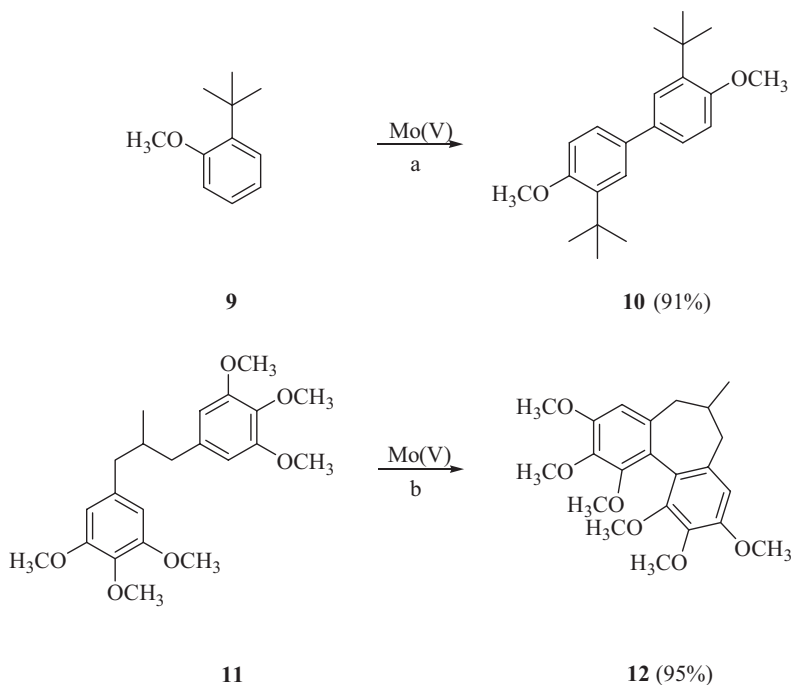
Many reagents, especially metal salts in high oxidation states, can effect electron transfer and induce the oxidative coupling process. The transformation might be also accomplished catalytically. These procedures are, however, strongly restricted to some substrates. Therefore, a stoichiometric procedure is the most useful for laboratory purposes [1]. Because the reaction rate has to be high to suppress several known side reactions to the desired biaryl formation (dealkylation, Fries-type rearrangements, proto-deiodination, overoxidation, quinol ether formation, etc.), only reagents which promote a rapid transformation are of synthetic value. Furthermore, many powerful reagents for this conversion involve highly toxic metal species, for example Tl(III), Hg(II), Pb(IV), and V(V). Beside the hazardous waste, the products might be contaminated by these toxic metals, which prohibits the synthesis of biologically active compounds. In addition, procedures for this particular transformation should be easy to perform, including removal of the biocompatible by-products. Only a few reagents fulfill these requirements – FeCl₃, phenyliodine(III) bis(trifluoroacetate), and MoCl₅.

The phenolic coupling can be mediated by different Fe(III) systems. For success of the transformation, the solubility of the reagents is crucial. BINOL (**2**) is efficiently formed from **1** when using the hexahydrate salt. This procedure will result in somewhat lower yields than many reports, but is easily scaled-up to a 5-molar scale [2]. Working in dichloromethane results in more electrophilic conditions which can be applied to more complex structures, for example **3** [3].

Kita et al. demonstrated that reagents based on hypervalent iodine also serve as efficient oxidative agents. The phenolic coupling and the non-phenolic transformation are performed in high yields [4]. Dichloromethane seems to be beneficial for the cationic conversion and enable rapid access to the coupling product **6**. In combination with Lewis acids, PIFA can be employed at low temperatures and accomplishes the transformation without affecting sensitive moieties which are usually not tolerated in the oxidative coupling process. PIFA was found to be the superior reagent for the dehydrodimerization of iodo arenes **7**, providing the corresponding multiple iodinated biaryls **8** [5].

**Scheme 2.** Oxidative phenol coupling reactions:(a) $\text{FeCl}_3 \cdot (\text{H}_2\text{O})_6$, THF, 40 °C, 3 h; (b) FeCl_3 , CH_2Cl_2 , 25 °C, 9 h.**Scheme 3.** Dehydrodimerization by phenyliodine(III)bis(trifluoroacetate): (a) PIFA, $\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , –40 °C, 1.5 h;(b) PIFA, $\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , 25 °C, 30 min.

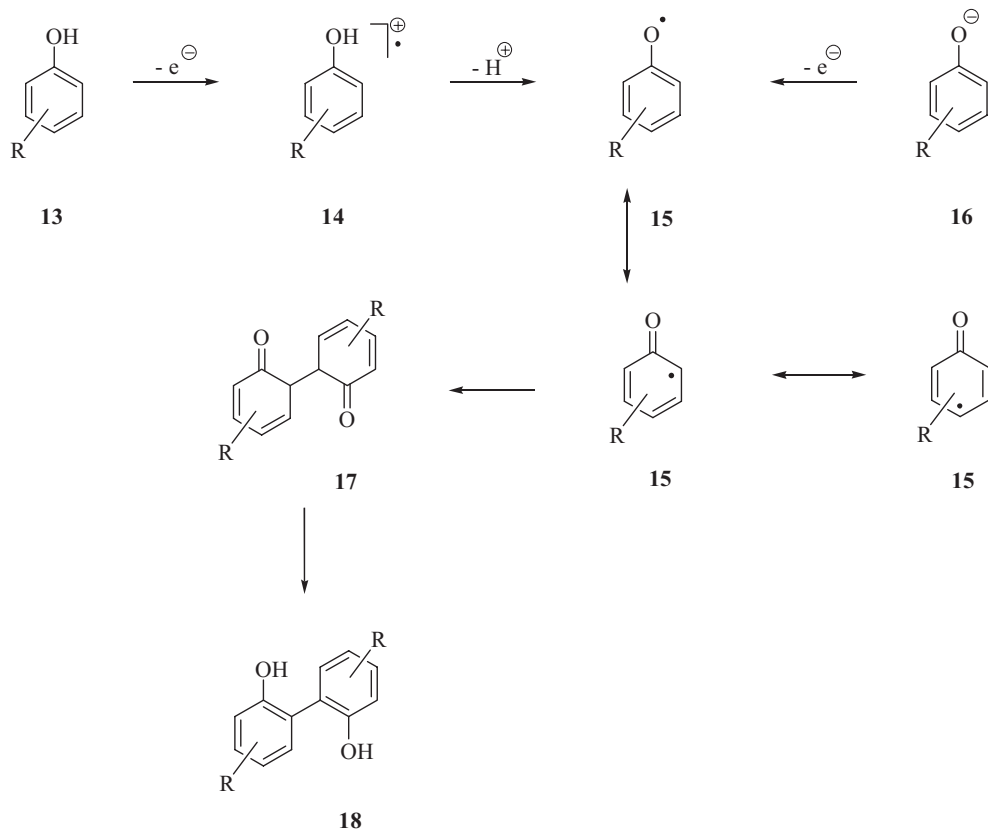
The high reaction rate of molybdenum pentachloride-mediated oxidative coupling reactions is compatible with alkyl groups that usually do not survive in strongly electrophilic media and give rise to *t*-butylated products (**10**) [6]. The oxidative cyclization reaction of **11** proceeds very smoothly when a MoCl₅/TiCl₄ mixture is applied, providing the seven-membered ring system **12** in excellent yields [7].



Scheme 4. Oxidative coupling reaction employing MoCl₅ systems: (a) MoCl₅, CH₂Cl₂, 0 °C, 30 min; (b) MoCl₅, TiCl₄, CH₂Cl₂, 0 °C, 50 min.

1.4.3.2 Mechanism

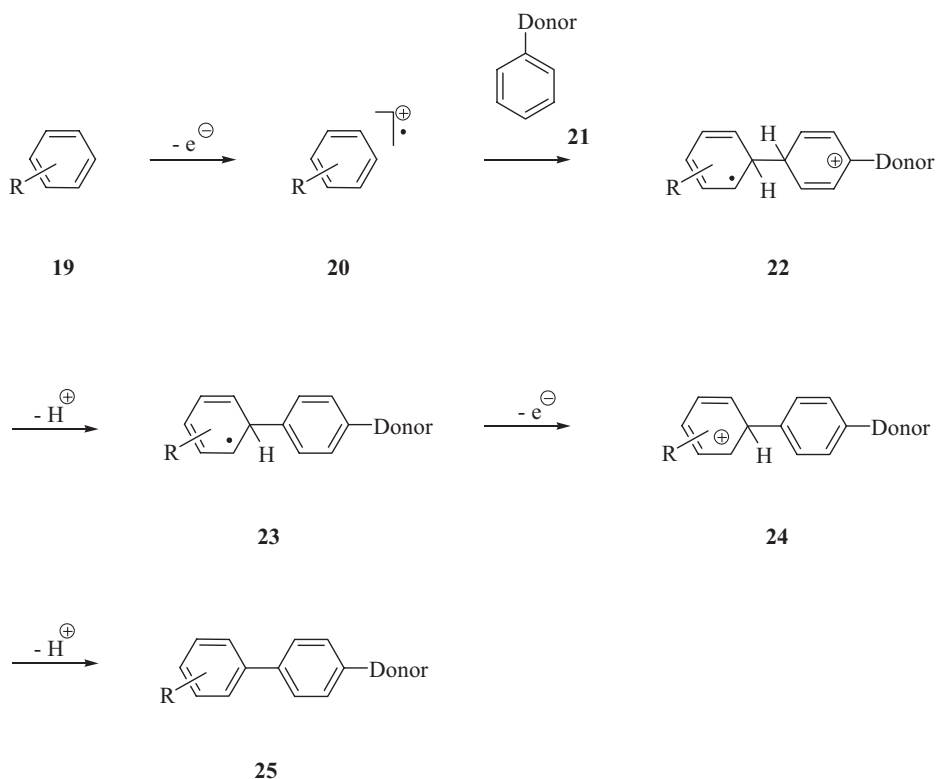
Depending on the media employed, phenols **13** can be directly oxidized to the corresponding radical cations **14**. The high acidity of this species enables the spontaneous loss of a proton providing the phenoxy radical **15**. Alternatively, **15** can be formed directly from the phenolate **16** by oxidation. This route to the phenoxy radical **15** is easier to perform and therefore preferred. The phenoxy radicals then undergo radical recombination resulting in the dimeric product **17**. Tautomeric processes furnish the biaryl system **18**. Because the intermediate **15** is mesomerically stabilized and has several potential reaction pathways, many coupling products are often obtained. The reaction conditions have a significant effect on product distribution.



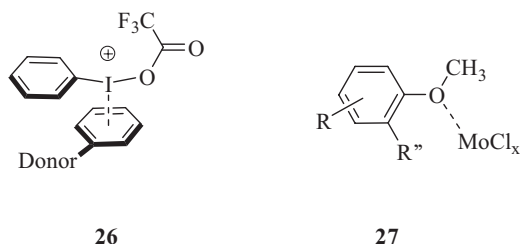
Scheme 5. Mechanism of the phenolic oxidative coupling reaction.

In the non-phenolic oxidative coupling reaction the electron-rich arene **19** undergoes electron transfer yielding the radical cation **20**, which is preferably treated in chlorinated solvents or strongly acidic media. Attack of **20** on the electron-rich reaction partner **21** will proceed in the same way as an electrophilic aromatic substitution involving adduct **22** which extrudes a proton. The intermediate radical **23** is subsequently oxidized to the cationic species **24** which forms the biaryl **25** by rearomatization. In contrast with the mechanism outlined in Scheme 5, two different oxidation steps are required.

For both modern reagents PIFA and MoCl_5 an inner-sphere radical transfer is expected, as depicted in Scheme 7. The Lewis acidic additives involved in the PIFA-mediated transformation create an iodonium species that forms a π -complex **26** with the substrate; this subsequently leads to an electron transfer. In contrast, the electrophilic molybdenum chloride most probably coordinates to the oxygen atoms of the donor functions which will then start the transformation. Smooth conversions are obtained if the substituent R'' adjacent to the donor (**27**) is another methoxy group or a bulky moiety.



Scheme 6. Dehydrodimerization of non-phenolic substrates.



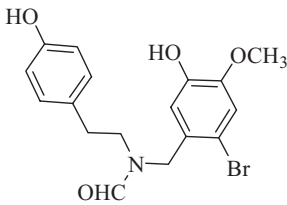
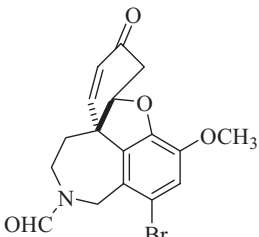
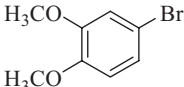
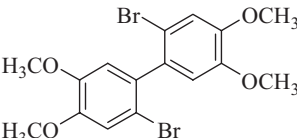
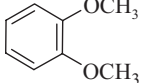
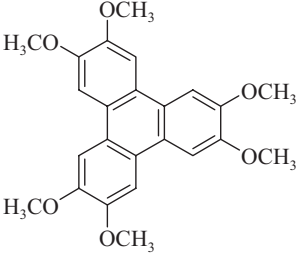
Scheme 7. Expected intermediates enabling inner-sphere radical transfer.

1.4.3.3 Scope and Limitations

The iron(III)-mediated oxidative coupling reaction is convenient to perform, because most of the reagents employed are inexpensive and readily available. In general, the yields obtained are sufficient but can be ameliorated when the conversion is performed heterogeneously. Unfortunately, labile moieties represented by secondary or tertiary alkyl, silyl, or iodo substituents will be shifted or lost during the transformation. For the phenolic coupling transformation, hydrated iron(III) salts or complex species, for example $K_3[Fe(CN)_6]$, can be used. The power of this

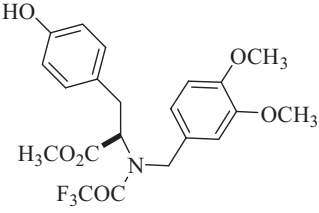
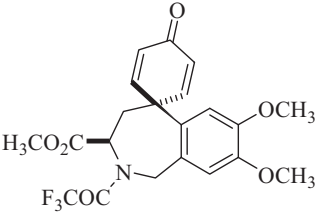
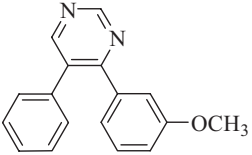
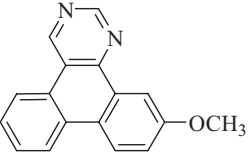
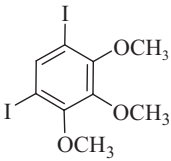
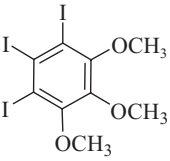
method is demonstrated in the large-scale route for the intermediate **29** in the galanthamine synthesis, which involves Michael-type addition after formation of a spirodienone moiety (Table 1) [8]. Oxidative treatment of non-phenolic substrates with iron based reagents requires more electrophilic conditions. The conversion of brominated veratrole **30** with anhydrous FeCl_3 results in the corresponding biaryl **31** [9]. The combination of ferrous chloride with sulfuric or acetic acid will increase the oxidative power and occasionally lead to partial dealkylation of donor functionalities. Hexamethoxytriphenylene **33** is obtained directly from the parent veratrole **32** when sulfuric acid is added [10].

Table 1. Examples of oxidative coupling with different Fe(III) systems.

Starting material	Product	Yield (%)	Ref.
 <p>28</p>	 <p>29</p>	45–50	8
 <p>30</p>	 <p>31</p>	85	9
 <p>32</p>	 <p>33</p>	98	10

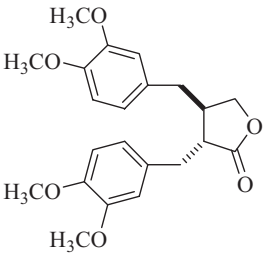
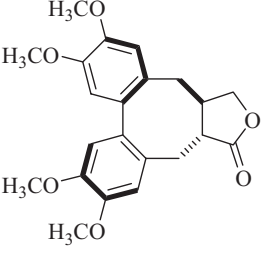
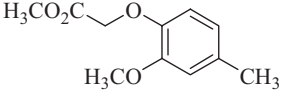
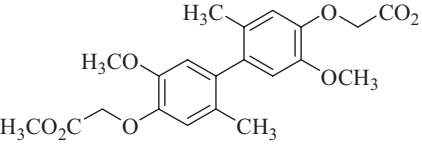
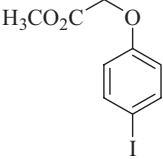
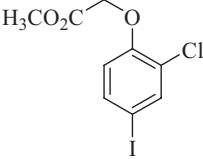
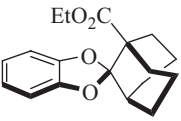
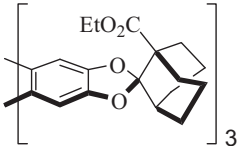
The hypervalent iodo compound PIFA is commercially available and is currently the most versatile reagent for oxidative arylations on a laboratory scale [11]. As the sole reagent, it can be used for the phenolic coupling reaction, which serves as a key transformation for natural product synthesis. Using fluorinated alcohols as solvents in the conversion of **34** turned out to be beneficial (Table 2) [12]. The combination of PIFA with a variety of Lewis acids creates a reliable reagent mixture that enables oxidative arylation of less activated systems **36** [13]. Although PIFA is known to be the best reagent for the dehydrodimerization of iodinated arenes, the treatment of very electron-rich iodo aryls **38** leads to halogen transfer by partial destruction of the aromatic substrate [5].

Table 2. Examples of PIFA-mediated transformations.

Starting material	Product	Yield (%)	Ref.
 <p>34</p>	 <p>35</p>	64	12
 <p>36</p>	 <p>37</p>	81	13
 <p>38</p>	 <p>39</p>	42	5

MoCl_5 has a short history as a reagent for the oxidative arylation reaction. It combines strong Lewis-acidic character with high oxidative power. It can, consequently, be successfully employed as the sole reagent in the key step for synthesis of the natural product **41** (Table 3) [14]. Enhancement of the reactivity is achieved

Table 3. Examples of the oxidative coupling reaction using MoCl_5 .

Starting material	Product	Yield (%)	Ref.
 <p style="text-align: center;">40</p>	 <p style="text-align: center;">41</p>	50	14
 <p style="text-align: center;">42</p>	 <p style="text-align: center;">43</p>	91	16
 <p style="text-align: center;">44</p>	 <p style="text-align: center;">45</p>	80	17
 <p style="text-align: center;">46</p>	 <p style="text-align: center;">47</p>	72	20

by combination with other Lewis acids, which essentially bind the by-product, hydrogen chloride [15]. The best results were obtained by employing Lewis acids such as TiCl_4 , because the electrophilic behavior of the MoCl_5 is not reduced. A variety of protective groups for the phenolic oxygen atoms, including silyl, substituted alkyl (42), and ketal moieties, were found to be compatible with the oxidative coupling process [16]. The use of alkoxycarbonylmethyl moieties accelerates the oxidative treatment with MoCl_5 and gives rise to chlorination reactions. Therefore, the first selective chlorination of iodobenzene 44 was realized [17]. Investigations

of biaryl formation from electron-rich benzenes revealed that a 1,2-dialkoxy-substitution pattern was beneficial; two equivalents of MoCl_5 are required for each C–C bond formation [18]. A variety of sensitive substituents are tolerated in this transformation [19]. The potential of the reagent is similar to that of PIFA. The oxidative trimerization of catechol ketals **46** to the corresponding triphenylene derivatives **47** was first accomplished by use of MoCl_5 [20].

Experimental

1,1'-Binaphthalene-2,2'-diol (BINOL, **2**)

Iron(III) chloride hexahydrate (21.6 g, 80 mmol) was dissolved in 13 mL tetrahydrofuran. After 20 min, 2-naphthol **1** (7.2 g, 50 mmol) was added and the reaction mixture was stirred at 80–85 °C for 3 h. The hot mixture was added dropwise to a solution of 20 g citric acid in 300 mL water, with vigorous stirring. The residue in the reaction flask was washed with 50 mL ethyl acetate. After 40 min the suspension was acidified with 30 mL conc. hydrochloric acid and extracted with ethyl acetate (2 × 70 mL). The combined organic layers were washed with 20 mL aqueous hydrochloric acid (10 %), water (2 × 40 mL), and the solvent was evaporated under reduced pressure. Toluene (20 mL) was added and again the solvent was evaporated. The crude product was recrystallized from 40 mL toluene. Standing at room temperature overnight yielded 4.0 g colorless crystals which were removed by filtration, washed with pentane, and dried under high vacuum. After evaporation of the filtrate and subsequent recrystallization from 10 mL toluene, another 500 mg pure product was obtained. Yield: 4.5 g (62 %); m.p. 216–218 °C. ^1H NMR (CDCl_3 , 300 MHz): δ = 5.21 (s, 2H, OH), 7.11–7.52 (m, 8H), 7.91 (d, 2H, J = 7.5 Hz), 7.99 (d, 2H, J = 8.8 Hz).

2,2',6,6'-Tetraiodo-3,3',4,4'-tetramethoxybiphenyl (**8**)

1,5-Diiodo-2,3-dimethoxybenzene (**7**; 585 mg, 1.50 mmol) was dissolved in 20 mL anhydrous dichloromethane. A solution of PIFA (323 mg, 0.75 mmol) and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.19 mL, 1.50 mmol) in 5 mL dichloromethane was added in small portions over a period of 15 min at 25 °C. After stirring for an additional 15 min, the solvent was evaporated under vacuum and without further work-up the crude mixture was directly subjected to column chromatography. TLC (silica, cyclohexane–ethyl acetate, 90:10): R_F = 0.27. On evaporation of the solvents, 439 mg (75 %) biaryl **8** was obtained as a colorless crystalline solid, m.p. >300 °C. ^1H NMR (CDCl_3 , 300 MHz): δ = 3.71 (s, 6H, OCH_3), 3.88 (s, 6H, OCH_3), 7.57 (s, 2H, CH).

3,3'-Di-*t*-butyl-4,4'-dimethoxybiphenyl (**10**)

MoCl_5 (1.09 g, 4.0 mmol) was dissolved in 20 mL anhydrous dichloromethane under an inert atmosphere and cooled to 0 °C. 2-*t*-Butyl anisole (**9**; 328 mg, 2.00 mmol) in 5 mL dichloromethane was added and the reaction mixture was stirred for 30 min at 0 °C. After quenching with 25 mL saturated NaHCO_3 solution, the aqueous layer was extracted with ethyl acetate (3 × 50 mL). Subsequent treatment with brine, anhydrous MgSO_4 , and concentration of the organic frac-

tion provided the crude product, which was purified by column chromatography on silica with cyclohexane–ethyl acetate, 95:5; R_F = 0.58. Biphenyl **10** (298 mg, 91 %), m.p. 124 °C (EtOH), was obtained as a light yellow solid on evaporation of the solvents. ^1H NMR (CDCl_3 , 300 MHz): δ = 1.43 (s, 18H, CH_3), 3.86 (s, 6H, OCH_3), 6.92 (d, J = 8.6 Hz, 2H, 5-H), 7.35 (dd, J = 8.6, 2.4 Hz, 2H, 6-H), 7.46 (d, J = 2.4 Hz, 2H, 2-H).

11H-9,10-Dihydro-10-methyl-2,3,4,5,6,7-hexamethoxydibenzo[*a,c*]cycloheptene (**12**)

Under anhydrous, inert conditions, **11** (1.00 g, 2.56 mmol) was dissolved in 30 mL dichloromethane. The chilled mixture (0 °C) was rapidly treated with TiCl_4 (0.53 mL, 4.87 mmol) and MoCl_5 (1.33 g, 4.87 mmol). The reaction mixture was then stirred for 50 min at 0 °C and subsequently fractionated between 150 mL ethyl acetate and sat. NaHCO_3 solution (2×100 mL). The aqueous phase was re-extracted with ethyl acetate. The combined organic phases were treated with brine (2×50 mL) and anhydrous MgSO_4 providing, on concentration, the crude product, which was purified by column chromatography on silica with cyclohexane–ethyl acetate, 80:20; R_F = 0.33. **12** (0.95 g, 95%) was obtained as slightly colored crystals, m.p. 139 °C. ^1H NMR (CDCl_3 , 400 MHz): δ = 0.95 (d, J = 9.2 Hz, 3H, 12-H), 1.80–1.87 (m, 1H, 9-/11- H_{eq}), 2.08–2.13 (m, 1H, 9-/11- H_{ax}), 2.25–2.34 (m, 1H, 10-H), 2.35–2.41 (m, 1H, 9-/11- H_{eq}), 2.47–2.54 (m, 1H; 9-/11- H_{ax}), 3.65, 3.66 (s, 6H, 4-H-, 5-H- OCH_3), 3.88, 3.89, 3.90, 3.91 (s, 12H, 2-, 3-, 6-, 7- OCH_3), 6.50, 6.55 (s, 2H, 1-, 8-H).

References to Chapter 1 – C–H Transformation at Arenes

References and Notes to Section 1.1

- 1 C. F. Cross, E. J. Bevan, T. Herberg, *Ber.* **1900**, 33, 2015.
- 2 C. Walling, R. A. Johnson, *J. Am. Chem. Soc.* **1975**, 97, 363.
- 3 J. H. Merz, W. A. Waters, *J. Chem. Soc.* **1949**, 2427.
- 4 C. Walling, D. M. Camaioni, S. S. Kim, *J. Am. Chem. Soc.* **1978**, 100, 4814.
- 5 J. Wellmann, E. Steckhan, *Chem. Ber.* **1977**, 110, 3561.
- 6 S. Udenfriend, C. T. Clark, J. Axelrod, B. B. Brodie, *J. Biol. Chem.* **1954**, 208, 731.
- 7 B. B. Brodie, J. Axelrod, P. A. Shore, S. Udenfriend, *J. Biol. Chem.* **1954**, 208, 741.
- 8 S. Ito, T. Yamasaki, H. Okada, S. Okino, K. Sasaki, *J. Chem. Soc., Perkin Trans. 2* **1988**, 285.
- 9 S. Ito, A. Kunai, H. Okada, K. Sasaki, *J. Org. Chem.* **1988**, 53, 296.
- 10 Y. Mao, A. Bakac, *Inorg. Chem.* **1996**, 35, 3925.
- 11 C. Walling, *Acc. Chem. Res.* **1998**, 31, 155.
- 12 J. O. Edwards, R. Curci, in *Catalytic Oxidations with Hydrogen Peroxide as Oxidant* (Ed.: G. Strukul), Kluwer Academic Publishers, **1992**, p. 97.
- 13 G. Sosnovsky, D. J. Rawlinson, in *Organic Peroxides*, Vol. 2 (Ed.: D. Swern), Wiley-Interscience, New York, **1971**, p. 269.
- 14 W. T. Dixon, R. O. C. Norman, *J. Chem. Soc.* **1964**, 4857.
- 15 E. A. Karakhanov, S. Y. Narin, T. Y. Filippova, A. G. Dedov, *Dokl. Akad. Nauk SSSR* **1987**, 292, 1387.
- 16 D. Bianchi, M. Bertoli, R. Tassinari, M. Ricci, R. Vignolo, *J. Mol. Catal. A: Chem.* **2003**, 204–205, 419.

- 17 D. Bianchi, R. Bortolo, R. Tassinari, M. Ricci, R. Vignolo, *Ang. Chem. Int. Ed.* **2000**, 39, 4321.
- 18 D. Bianchi, M. Bertoli, R. Tassinari, M. Ricci, R. Vignolo, *J. Mol. Catal. A: Chem.* **2003**, 200, 111.
- 19 J. R. L. Smith, B. A. J. Shaw, D. M. Foulkes, A. M. Jeffrey, D. M. Jerina, *J. Chem. Soc., Perkin Trans. D* **1977**, 1583.
- 20 H. Mimoun, L. Saussine, E. Daire, M. Postel, J. Fischer, R. Weiss, *J. Am. Chem. Soc.* **1983**, 105, 3101.
- 21 G. B. Shul'pin, D. Attanasio, L. Suber, *J. Catal.* **1993**, 142, 147.
- 22 M. Bianchi, M. Bonchio, V. Conte, F. Coppa, F. Di Furia, G. Modena, S. Moro, S. Standen, *J. Mol. Catal.* **1993**, 83, 107.
- 23 M. Bonchio, V. Conte, F. Di Furia, G. Modena, S. Moro, *J. Org. Chem.* **1994**, 59, 6262.
- 24 E. Hata, T. Takai, T. Yamada, T. Mukaiyama, *Chem. Lett.* **1994**, 1849.
- 25 E. Battistel, R. Tassinari, M. Fornaroli, L. Bonoldi, *J. Mol. Catal. A: Chem.* **2003**, 202, 107.
- 26 G. B. Shul'pin, E. R. Lachter, *J. Mol. Catal. A: Chem.* **2003**, 197, 65.
- 27 G. A. Olah, R. Ohnishi, *J. Org. Chem.* **1978**, 43, 865.
- 28 M. E. Kurz, G. J. Johnson, *J. Org. Chem.* **1971**, 36, 3184.
- 29 E. J. Behrman, in *Organic Reactions*, Vol. 35, John Wiley and Sons, New York, **1988**, p. 421.
- 30 E. J. Behrman, *Biochem. J.* **1982**, 201, 677.
- 31 A. Marsella, S. Agapakis, F. Pinna, G. Strukul, *Organometallics* **1992**, 11, 3578.
- 32 T. Jintoku, H. Taniguchi, Y. Fujiwara, *Chem. Lett.* **1987**, 1865.
- 33 T. Jintoku, K. Nishimura, K. Takaki, Y. Fujiwara, *Chem. Lett.* **1990**, 1687.
- 34 A. Kunai, T. Wani, Y. Uehara, F. Iwasaki, Y. Kuroda, S. Ito, K. Sasaki, *Bull. Chem. Soc. Jpn.* **1989**, 62, 2613.
- 35 L. C. Passoni, A. T. Cruz, R. Buffon, U. Schuchardt, *J. Mol. Catal. A: Chem.* **1997**, 120, 117.
- 36 F. Shibahara, S. Kinoshita, K. Nozaki, *Org. Lett.* **2004**, 6, 237.
- 37 T. Jintoku, K. Takaki, Y. Fujiwara, Y. Fuchita, K. Hiraki, *Bull. Chem. Soc. Jpn.* **1990**, 63, 438.
- 38 Y. Fuchita, K. Hiraki, Y. Kamogawa, M. Suenaga, K. Tohgoh, Y. Fujiwara, *Bull. Chem. Soc. Jpn.* **1989**, 62, 1081.
- 39 M. Makosza, K. Sienkiewicz, *J. Org. Chem.* **1998**, 63, 4199.
- 40 K. Fujimoto, Y. Tokuda, H. Maekawa, Y. Matsubara, T. Mizuno, I. Nishiguchi, *Tetrahedron* **1996**, 52, 3889.
- 41 R. H. Thomson, in *The Chemistry of Quinonoid Compounds*, Vol. 1 (Ed.: S. Patai), John Wiley and Sons, **1974**, p. 111.
- 42 M. Periasamy, M. V. Bhatt, *Synthesis* **1977**, 330.
- 43 W. Adam, W. A. Herrmann, J. Lin, C. R. Saha-Moeller, R. W. Fischer, J. D. G. Correia, *Ang. Chem. Int. Ed. Engl.* **1994**, 33, 2475.
- 44 W. A. Herrmann, J. J. Haider, R. W. Fischer, *J. Mol. Catal. A: Chem.* **1999**, 138, 115.
- 45 R. Song, A. Sorokin, J. Bernadou, B. Meunier, *J. Org. Chem.* **1997**, 62, 673.
- 46 W. Adam, W. A. Herrmann, J. Lin, C. R. Saha-Moeller, *J. Org. Chem.* **1994**, 59, 8281.
- 47 W. Adam, W. A. Herrmann, C. R. Saha-Moeller, M. Shimizu, *J. Mol. Catal. A: Chem.* **1995**, 97, 15.
- 48 R. Saladino, V. Neri, E. Mincione, S. Marini, M. Coletta, C. Fiorucci, P. Filippone, *J. Chem. Soc., Perkin Trans. 1* **2000**, 581.
- 49 H. Sun, K. Harms, J. Sundermeyer, *J. Am. Chem. Soc.* **2004**, 126, 9550.

References and Notes to Section 1.2.1

- 1 (a) P. M. Esteves, J. Walkimar de Carneiro, S. P. Cardoso, A. G. H. Barbosa, K. K. Laali, G. Rasul, G. K. S. Prakash, G. A. Olah, *J. Am. Chem. Soc.* **2003**, 125, 4836–4849; (b) R. Taylor, *Electrophilic Aromatic Substitution*, John Wiley & Sons, USA, **1990**.
- 2 (a) M. R. Crampton, *Organic Reaction Mechanisms*, A. C. Knipe, W. E. Watts (Eds.), **2004**, John Wiley & Sons, UK, pp. 283–294; (b) M. Makosza,

- W. Wojciechowski, *Heterocycles* **2001**, 54, 445–474.
- 3 R. A. Rossi, A. B. Pierini, A. B. Penenory, *Chem. Rev.* **2003**, 103, 71–167.
 - 4 (a) M. Makosza, A. Kwast, *Eur. J. Org. Chem.* **2004**, 10, 2125–2130;
(b) M. Makosza, T. Lemek, A. Kwast, F. Terrier, *J. Org. Chem.* **2002**, 67, 394–400.
 - 5 (a) J. Clayden, *The Chemistry of Organolithium Compounds*, Z. Rappoport, I. Marek (Eds.), John Wiley & Sons, UK, **2004**, pp. 495–646; (b) C. G. Hartung and V. Snieckus, *Modern Arene Chemistry*, D. Astruc (Ed.), Wiley–VCH, USA, **2002**, pp. 330–367; (c) V. Snieckus, *Chem. Rev.* **1990**, 90, 879–933.
 - 6 (a) S. Murai, Ed. *Activation of Unreactive Bonds and Organic Synthesis*, Vol 3, Springer, Germany, **1999**;
(b) F. Kakiuchi, S. Murai, *Acc. Chem. Res.* **2002**, 35, 826–834.
 - 7 New developments: A. G. M. Barrett, N. Boulouc, D. C. Braddock, D. Chadwick, D. A. Henderson, *Synlett* **2002**, 1653–1656 and refs cited therein.
 - 8 R. J. Mills, V. Snieckus, *Tetrahedron Lett.* **1984**, 25, 483–486.
 - 9 B. A. Chauder, A. V. Kalinin, V. Snieckus, *Synthesis* **2001**, 140–144.
 - 10 R. J. Mills, N. J. Taylor, V. Snieckus, *J. Org. Chem.* **1989**, 54, 4372–4385.
 - 11 M. P. Sibi, V. Snieckus, *J. Org. Chem.* **1983**, 48, 1935–1937.
 - 12 M. P. Sibi, S. Chattopadhyay, J. W. Dankwardt, V. Snieckus, *J. Am. Chem. Soc.* **1985**, 107, 6312–6315.
 - 13 A. V. Kalinin, A. J. M. Da Silva, C. C. Lopes, R. S. C. Lopes, V. Snieckus, *Tetrahedron Lett.* **1998**, 39, 4995–4998.
 - 14 B. A. Chauder, A. V. Kalinin, N. J. Taylor, V. Snieckus, *Angew. Chem. Int. Ed.* **1999**, 38, 1435–1438.
 - 15 M. C. Whisler, S. MacNeil, V. Snieckus, P. Beak, *Angew. Chem. Int. Ed.* **2004**, 43, 2206–2225.
 - 16 (a) E. J.-G. Anttil, V. Snieckus, *J. Organomet. Chem.* **2002**, 653, 150–160;
(b) E. J.-G. Anttil, V. Snieckus, *Metal-Catalyzed Cross-Coupling Reactions*, 2nd Ed., F. Diederich, A. de Meijere (Eds.), Wiley–VCH, Germany, **2004**, pp. 761–813.
 - 17 J. A. McCubbin, X. Tong, W. Ruiyao, Y. Zhao, V. Snieckus, R. P. Lemieux, *J. Am. Chem. Soc.* **2004**, 126, 1161–1167.
 - 18 W. Wang, V. Snieckus, *J. Org. Chem.* **1992**, 57, 424–426.
 - 19 M. Watanabe, M. Sahara, M. Kubo, S. Furukawa, R. J. Billedeau, V. Snieckus, *J. Org. Chem.* **1984**, 49, 742–747.
 - 20 R. J. Mills, V. Snieckus, *J. Org. Chem.* **1983**, 48, 1565–1568.
 - 21 J. A. Turner, *J. Org. Chem.* **1983**, 48, 3401–3408.
 - 22 (a) S. Yu, C. Rabalakos, W. D. Mitchell, W. D. Wulff, *Org. Lett.* **2005**, 7, 367–369;
(b) M. P. Sibi, J. W. Dankwardt, V. Snieckus, *J. Org. Chem.* **1986**, 51, 271–273.
 - 23 Z. Zhao, V. Snieckus, *Org. Lett.* **2005**, submitted.
 - 24 T. Kremer, M. Junge, P. v. R. Schleyer, *Organomet.* **1996**, 15, 3345–3359.
 - 25 R. A. Gossage, T. B. H. Jastrzebski, G. van Koten, *Angew. Chem. Int. Ed.* **2005**, 44, 1448–1454.
 - 26 G. Queguiner, F. Marsais, V. Snieckus, J. Epszajn, *Adv. Heterocycl. Chem.* **1991**, 52, 187–304.
 - 27 R. R. Fraser, M. Bresse, T. S. Mansour, *J. Am. Chem. Soc.* **1983**, 105, 7790–7791.
 - 28 (a) M. Uchiyama, H. Naka, Y. Matsumoto, T. Ohwada, *J. Am. Chem. Soc.* **2004**, 126, 10526–10527;
(b) M. Uchiyama, T. Miyoshi, Y. Kajihara, T. Sakamoto, Y. Otani, T. Ohwada, Y. Kondo, *J. Am. Chem. Soc.* **2002**, 124, 8514–8515; (c) P. B. Kisanga, J. G. Verkade, R. Schwessinger, *J. Org. Chem.* **2000**, 65, 5431–5432.
 - 29 P. Beak, T. J. Musick, C. Liu, T. Cooper, D. J. Gallagher, *J. Org. Chem.* **1993**, 58, 7330–7335.
 - 30 G. E. Keck, T. T. Wager, J. F. D. Rodriguez, *J. Am. Chem. Soc.* **1999**, 121, 5176–5190.
 - 31 M. P. Sibi, K. Shankaran, B. I. Alo, W. R. Hahn, V. Snieckus, *Tetrahedron Lett.* **1987**, 28, 2933–2936.
 - 32 S. O. De Silva, I. Ahmad, V. Snieckus, *Can. J. Chem.* **1979**, 57, 1598–1605.
 - 33 S. O. De Silva, J. N. Reed, R. J. Billedeau, X. Wang, D. J. Norris, V. Snieckus, *Tetrahedron* **1992**, 48, 4863–4878.

- 34 T. K. Macklin, V. Snieckus, unpublished results.
- 35 P. Stanetty, B. Krumpak, *J. Org. Chem.* **1996**, 61, 5130–5133.
- 36 H. Butenschoen, M. Winkler, K. P. C. Vollhardt, *J. Chem. Soc., Chem. Comm.* **1986**, 388–390.
- 37 S. Danishefsky, J. Y. Lee, *J. Am. Chem. Soc.* **1989**, 111, 4829–4837.
- 38 (a) Y. S. Lo, L. T. Rossano, D. J. Meloni, J. R. Moore, Y. –C. Lee, J. F. Arneett, *J. Heterocycl. Chem.* **1995**, 32, 355–357; (b) R. D. Larsen, A. O. King, C. Y. Chen, E. G. Corley, B. S. Foster, F. E. Roberts, C. Yang, D. R. Lieberman, R. A. Reamer, D. M. Tschaen, T. R. Verhoeven, P. J. Reider, *J. Org. Chem.* **1994**, 59, 6391–6394.
- 12 H. C. Brown, R. A. Wirkkala, *J. Am. Chem. Soc.*, **1966**, 88, 1447.
- 13 G. B. Deacon, G. J. Farquharson, *J. Organomet. Chem.*, **1974**, 67, C1.
- 14 V. I. Bregadze, V. Ts. Kampel, N. N. Godovikov, *J. Organomet. Chem.*, **1976**, 112, 249.
- 15 G. A. Olah, S. H. Yu, D. G. Parker, *J. Org. Chem.*, **1976**, 41, 1983 and references cited therein.
- 16 W. Lau, J. K. Kochi, *J. Am. Chem. Soc.*, **1986**, 108, 6720 and reference cited therein.
- 17 W. Lau, J. C. Huffman, J. K. Kochi, *J. Am. Chem. Soc.*, **1982**, 104, 5515.
- 18 L. C. Damude, P. A. W. Dean, *J. Organomet. Chem.*, **1979**, 181, 1. L. C. Damude, P. A. W. Dean, M. D. Sefcik, J. Schaeffer, *J. Organomet. Chem.*, **1982**, 226, 105.
- 19 A. S. Borovik, S. G. Bott, A. R. Barron, *Angew. Chem. Int. Ed.*, **2000**, 39, 4117; *J. Am. Chem. Soc.*, **2001**, 123, 11219. A. S. Borovik, A. R. Barron, *J. Am. Chem. Soc.*, **2002**, 124, 3743. C. S. Branch, A. R. Barron, *J. Am. Chem. Soc.*, **2002**, 124, 14156.
- 20 M. R. Haneline, M. Tsunoda, F. P. Gabbai, *J. Am. Chem. Soc.*, **2002**, 124, 3737. M. R. Haneline, J. B. King, F. P. Gabbai, *Dalton*, **2003**, 2686.
- 21 J. K. Kochi, *Angew. Chem. Int. Ed. Engl.*, **1988**, 27, 1227.
- 22 A. G. Davies, D. C. McGuchan, *Organometallics*, **1991**, 10, 329. A. G. Davies, K. M. Ng, *J. Chem. Soc., Perkin Trans. 2*, **1998**, 2599.
- 23 L. Buzhansky, B.-A. Feit, *J. Org. Chem.*, **2002**, 67, 7523.
- 24 H. Gilman, R. K. Abbott, Jr., *J. Am. Chem. Soc.*, **1943**, 65, 122.
- 25 V. P. Glushkova, K. A. Kocheshkov, *Dokl. Akad. Nauk SSSR*, **1957**, 116, 233.
- 26 A. McKillop, J. D. Hunt, M. J. Zelesko, J. S. Fowler, E. C. Taylor, G. McGillivray, F. Kienzle, *J. Am. Chem. Soc.*, **1971**, 93, 4841. E. C. Taylor, F. Kienzle, R. L. Robey, A. McKillop, J. D. Hunt, *J. Am. Chem. Soc.*, **1971**, 93, 4845.
- 27 A. McKillop, E. C. Taylor, *Adv. Organometal. Chem.*, **1973**, 11, 147.
- 28 S. Uemura, *Synth. Reagents*, **1983**, 5, 165.
- 29 A. Ya. Usyatinskii, V. I. Bregadze, *Russ. Chem. Rev.*, **1988**, 57, 1054.

References and Notes to Section 1.2.2

- 1 J. Volhard, *Liebigs Ann. Chem.*, **1892**, 267, 172.
- 2 L. Pesci, *Gazz. Chim. Ital.*, **1892**, 22, 373; **1893**, 23, 521; *Z. Anorg. Allg. Chem.*, **1897**, 15, 208.
- 3 O. Dimroth, *Ber. Dtsch. Chem. Ges.*, **1898**, 31, 2154; **1899**, 32, 758; **1902**, 35, 2032, 2853.
- 4 A. E. Shilov, G. B. Shul'pin, *Activation and Catalytic Reactions of Saturated Hydrocarbons in the Presence of Metal Complexes*, Kluwer Academic Publishers, Dordrecht, **2000**.
- 5 M. Wills, *Contemp. Org. Synth.*, **1996**, 3, 201.
- 6 R. Taylor, *Electrophilic Aromatic Substitution*; Wiley, New York, **1990**.
- 7 L. G. Makarova, A. N. Nesmeyanov, *Organic Compounds of Mercury*, North-Holland, Amsterdam, **1967**.
- 8 W. Kitching, *Organometal. Chem. Rev.*, **1968**, 3, 35.
- 9 A. J. Bloodworth, *The Organic Chemistry of Mercury*, C. A. McAuliffe, Ed., Macmillan, London, **1977**. R. C. Larock, *Organomercury Compounds in Organic Synthesis*, Springer-Verlag, Berlin, **1985**.
- 10 V. I. Boev, A. I. Moskalenko, A. M. Boev, *Russ. Chem. Rev.*, **1997**, 66, 789.
- 11 D. K. Breiting, *Synth. Methods Organomet. Inorg. Chem.*, **1999**, 5, 193; *Compr. Coord. Chem. II*, **2004**, 6, 1253.

- 30 H. M. C. Ferraz, L. F. Silva Jr., T. de O. Vieira, *Synthesis*, **1999**, 2001.
- 31 W. Lau, J. K. Kochi, *J. Am. Chem. Soc.*, **1984**, 106, 7100.
- 32 E. C. Taylor, E. C. Bigham, D. K. Johnson, A. Mckillop, *J. Org. Chem.*, **1977**, 42, 362.
- 33 V. V. Grushin, *Chem. Eur. J.*, **2002**, 8, 1006.
- 34 J. T. Pinhey, *Aust. J. Chem.*, **1991**, 44, 1353; *Lead. In: Comprehensive Organometallic Chemistry II*, E. W. Abel, F. G. A. Stone, G. Wilkinson, Eds., 1995, Vol. 11, 461; *Pure Appl. Chem.* **1996**, 68, 819.
- 35 M. G. Moloney, *Main Group Metal Chem.*, **2001**, 24, 653.
- 36 G. I. Elliott, J. P. Konopelski, *Tetrahedron*, **2001**, 57, 5683.
- 37 P. J. Guiry, P. J. McCormack, *Sci. Synth.*, **2003**, 5, 673.
- 38 E. M. Panov, K. A. Kocheshkov, *Dokl. Akad. Nauk SSSR*, **1958**, 123, 295. F. R. Preuss, R. Menzel, *Arch. Pharm.*, **1958**, 291, 350.
- 39 L. C. Willemssens, D. De Vos, J. Spierenburg, J. Wolters, *J. Organometal. Chem.*, **1972**, 39, C61.
- 40 L. M. Stock, T. L. Wright, *J. Org. Chem.*, **1980**, 45, 4645.
- 41 J. R. Kalman, J. T. Pinhey, S. Sternhell, *Tetrahedron Lett.* **1972**, 5369.
- 42 D. M. X. Donnelly, J.-P. Finet, J. M. Kiely, *Tetrahedron Lett.*, **1991**, 31, 3835.
- 43 V. V. Grushin, W. J. Marshall, D. L. Thorn, *Adv. Synth. Catal.*, **2001**, 343, 433.
- 44 D. Seyferth, M. O. Nestle, *J. Am. Chem. Soc.*, **1981**, 103, 3320.
- 45 B. K. Nicholson, S. K. Whitley, *J. Organomet. Chem.*, **2004**, 689, 515.
- 4 J.-Y. Cho, C. N. Iverson, M. R. Smith, III., *J. Am. Chem. Soc.* **2000**, 122, 12868–12869.
- 5 J.-Y. Cho, M. K. Tse, D. Holmes, R. E. Maleczka, Jr., M. R. Smith, III., *Science* **2002**, 295, 305–308.
- 6 T. Ishiyama, J. Takagi, K. Ishida, N. Miyauro, N. R. Anastasi, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, 124, 390–391.
- 7 J. Takagi, K. Sato, J. F. Hartwig, T. Ishiyama, N. Miyauro, *Tetrahedron Lett.* **2002**, 43, 5649–5651.
- 8 T. Ishiyama, J. Takagi, J. F. Hartwig, N. Miyauro, *Angew. Chem., Int. Ed.* **2002**, 41, 3056–3058.
- 9 T. Ishiyama, J. Takagi, Y. Yonekawa, J. F. Hartwig, N. Miyauro, *Adv. Synth. Catal.* **2003**, 345, 1103–1106.
- 10 T. Ishiyama, Y. Nobuta, J. F. Hartwig, N. Miyauro, *Chem. Commun.* **2003**, 2924–2925.
- 11 P. Nguyen, H. P. Blom, S. A. Westcott, N. J. Taylor, T. B. Marder, *J. Am. Chem. Soc.* **1993**, 115, 9329–9330.
- 12 H. Tamura, H. Yamazaki, H. Sato, S. Sakaki, *J. Am. Chem. Soc.* **2003**, 125, 16114–16126.
- 13 R. Uson, L. A. Oro, J. A. Cabeza, *Inorg. Synth.* **1985**, 23, 126–130.

References to Section 1.2.4

- 1 F. Kakiuchi, N. Chatani, *Adv. Synth. Catal.* **2003**, 345, 1077–1101.
- 2 W. A. Gustavson, P. S. Epstein, M. D. Curtis, *Organometallics* **1982**, 1, 884–885.
- 3 P. I. Djurovich, A. R. Dolich, D. H. Berry, *J. Chem. Soc., Chem. Commun.* **1994**, 1897–1898.
- 4 K. Ezbiatsky, P. I. Djurovich, M. LaForest, D. J. Sinning, R. Zayes, D. H. Berry, *Organometallics* **1998**, 17, 1455–1457.
- 5 Y. Uchimar, A. M. M. El Sayed, M. Tanaka, *Organometallics* **1993**, 12, 2065–2069.
- 6 F. Kakiuchi, K. Igi, M. Matsumoto, N. Chatani, S. Murai, *Chem. Lett.* **2001**, 422–423.
- 7 F. Kakiuchi, K. Igi, M. Matsumoto, T. Hayamizu, N. Chatani, S. Murai, *Chem. Lett.* **2002**, 396–397.

References and Notes to Section 1.2.3

- 1 T. Ishiyama, N. Miyauro, *J. Organomet. Chem.* **2003**, 680, 3–11.
- 2 T. Ishiyama, N. Miyauro, *Chem. Rec.* **2004**, 3, 271–280.
- 3 C. N. Iverson, M. R. Smith, III., *J. Am. Chem. Soc.* **1999**, 121, 7696–7697.

- 8 F. Kakiuchi, M. Matsumoto, K. Tsuchiya, K. Igi, T. Hayamizu, N. Chatani, S. Murai, *J. Organomet. Chem.* **2003**, 686, 134–144.
- 9 F. Kakiuchi, K. Tsuchiya, M. Matsumoto, E. Mizushima, N. Chatani, *J. Am. Chem. Soc.* in press.
- 10 M. Ishikawa, S. Okazaki, A. Naka, H. Sakamoto, *Organometallics* **1992**, 11, 4135–4139; M. Shikawa, A. Naka, *Synlett* **1995**, 795–802; A. Naka, K. K. Lee, K. Yoshizawa, T. Yamabe, M. Ishikawa, *Organometallics* **1999**, 18, 4524.
- 11 N. A. Williams, Y. Uchimar, M. Tanaka, *Dalton Trans.* **2003**, 236–243.
- 12 F. Kakiuchi, M. Matsumoto, M. Sonoda, T. Fukuyama, N. Chatani, S. Murai, N. Furukawa, Y. Seki, *Chem. Lett.* **2000**, 750–751.

References and Notes to Section 1.3.1.1

- 1 G. Dyker, E. Muth, A. S. K. Hashmi, L. Ding, *Adv. Synth. Catal.* **2003**, 345, 1247–1252.
- 2 M. M. Alam, M. Mujahid, R. Varala, S. R. Adapa, *Tetrahedron Lett.* **2003**, 44, 5115–5119.
- 3 For other catalysts such as CeCl_3 and InCl_3 , see: G. Bartoli, M. Bartolacci, M. Bosco, G. Foglia, A. Giuliani, E. Marcantoni, L. Sambri, E. Torregiani, *J. Org. Chem.* **2003**, 68, 4594–4597; J. S. Yadav, S. Abraham, B. V. S. Reddy, G. Sabitha, *Synthesis* **2001**, 2165–2169; K. Manabe, N. Aoyama, S. Kobayashi, *Adv. Synth. Catal.* **2001**, 343, 174–176; N. Srivastava, B. K. Banik, *J. Org. Chem.* **2003**, 68, 2109–2114; G. Dujardin, J.-M. Poirier, *Bull. Soc. Chim. France* **1994**, 131, 900–909.
- 4 Y. Nishibayashi, Y. Inada, M. Yoshikawa, M. Hidai, S. Uemura, *Angew. Chem. Int. Ed.* **2003**, 42, 1495–1498.
- 5 G. Dyker, E. Muth, unpublished results.
- 6 J. J. Kennedy-Smith, L. A. Young, F. D. Toste, *Org. Lett.* **2004**, 6, 1325–1327.

References and Notes to Section 1.3.1.2

- 1 (a) G. A. Olah, “Friedel–Crafts and Related Reactions” Wiley-Interscience, New York, (1964). Vol. 1; (b) H. Heaney, In “Comprehensive Organic Synthesis,” ed by B. M. Trost, I. Fleming, Pergamon Press, Oxford (1991), p. 733.
- 2 Examples of early trials, (a) M. Hino, K. Arata, *Chem. Lett.* **1978**, 325; (b) K. Nomita, Y. Sugaya, S. Sasa, M. Miwa *Bull. Chem. Soc. Jpn.* **1980**, 53, 2089; (c) T. Yamaguchi, A. Mitoh, K. Tanabe, *Chem. Lett.* **1982**, 1229; (d) F. Effenberger, G. Epple, *Angew. Chem. Int. Ed.* **1972**, 11, 300; (e) T. Mukaiyama, H. Nagaoka, M. Ohshima, M. Murakami, *Chem. Lett.* **1986**, 165; (f) F. Effenberger, D. Steegmiller, *Chem. Ber.* **1988**, 121, 117; (g) T. Mukaiyama, T. Ohno, T. Nishimura, S. J. Han, S. Kobayashi, *Chem. Lett.* **1991**, 1059.
- 3 For example, (a) J. O. Morley, *J. Chem. Soc. Perkin Trans. 2* **1977**, 601; (b) G. Harvey, G. Mader, *Collect. Czech. Chem. Commun.* **1992**, 57, 862; (c) D. E. Akporiaye, K. Daasvatn, J. Solberg, M. Stocker, *Stud. Surf. Sci. Catal.* **1993**, 78, 521; (d) H. van Bekkum, A. J. Hoefnagel, M. A. van Koten, E. A. Gunnewegh, A. H. G. Vogt, H. W. Kouwenhoven, *Stud. Surf. Sci. Catal.* **1994**, 83, 379; (e) F. Richard, H. Carreyre, G. Perot, *J. Catal.* **1996**, 159, 427; (f) A. K. Pandey, A. P. Singh, *Catal. Lett.* **1997**, 44, 129; (g) K. Smith, Z. Zhenhua, P. K. G. Hodgson, *J. Mol. Catal. A: Chem.* **1998**, 134, 121; (h) B. Jacob, S. Sugunan, A. P. Singh, *J. Mol. Catal. A: Chem.* **1999**, 139, 43; (i) S. Fujiyama and T. Kasahara, *Hydrocarbon Process* **1978**, 57, 147.
- 4 (a) S. Kobayashi, *Synlett* **1994**, 689; (b) S. Kobayashi, M. Sugiura, H. Kitagawa, W. W.-L. Lam, *Chem. Rev.* **2002**, 102, 2227; (c) S. Kobayashi, *Chem. Lett.* **1991**, 2187; (d) S. Kobayashi, I. Hachiya, *J. Org. Chem.* **1994**, 59, 3590.
- 5 (a) A. Kawada, S. Mitamura, J.-I. Matsuo, T. Tsuchiya, S. Kobayashi, *Bull. Chem. Soc. Jpn.* **2000**, 73, 2325; (b) A. Kawada, S. Mitamura,

- S. Kobayashi, *J. Chem. Soc. Chem. Commun.* **1993**, 1157; (c) A. Kawada, S. Mitamura, S. Kobayashi, *Synlett* **1994**, 545; (d) A. Kawada, S. Mitamura, S. Kobayashi, *J. Chem. Soc. Chem. Commun.* **1996**, 183.
- 6 (a) S. Kobayashi, *Eur. J. Org. Chem.* **1999**, 15; (b) S. Kobayashi, I. Hachiya, M. Araki, H. Ishitani, *Tetrahedron Lett.* **1993**, 34, 3755.
- 7 F. A. Cotton, G. Wilkinson, "Advanced Inorganic Chemistry, Fifth Edition," John Wiley and Sons, New York, 1988, p. 973.
- 8 (a) G. A. Olah, S. J. Kuhn, W. S. Tolgyesi, E. B. Becker, *J. Am. Chem. Soc.* **1962**, 84, 2733; (b) G. A. Olah, S. J. Kuhn, S. H. Flood, B. A. Hardie, *J. Am. Chem. Soc.* **1964**, 86, 2203; (c) G. A. Olah, M. B. Comisarow, *J. Am. Chem. Soc.* **1968**, 88, 3313.
- 9 (a) H. Burton, P. F. G. Praill, *J. Chem. Soc.* **1950**, 1203; (b) H. Burton, P. F. G. Praill, *J. Chem. Soc.* **1950**, 2034; (c) H. Burton, P. F. G. Praill, *J. Chem. Soc.* **1951**, 522; (d) H. Burton, P. F. G. Praill, *J. Chem. Soc.* **1951**, 529; (e) A. M. Avedikian, A. Kergomard, J. C. Tardivat, and J. P. Vullerme, *Bull. Soc. Chim. Fr.* **1974**, 11, 2652; (f) K. Baum, C. D. Beard, *J. Org. Chem.* **1975**, 40, 81.
- 10 (a) T. Mukaiyama, K. Suzuki, S. J. Han, S. Kobayashi, *Chem. Lett.* **1992**, 435; (b) I. Hachiya, M. Moriwaki, S. Kobayashi, *Bull. Chem. Soc. Jpn.* **1995**, 68, 2053.
- 11 For example, (a) S. Kobayashi, S. Iwamoto, *Tetrahedron Lett.* **1998**, 39, 4697; (b) J. Matsuo, K. Odashima, S. Kobayashi, *Synlett* **2000**, 403; (c) S. Kobayashi, I. Komoto, J.-I. Matsuo, *Adv. Synth. Catal.* **2001**, 343, 71; (d) J. R. Desmurs, M. Labrouillere, C. Le Roux, H. Gaspard, A. Laporterie, J. Dubac, *Tetrahedron Lett.* **1997**, 38, 8871.
- 2 M. Bandini, A. Melloni, A. Umani-Ronchi, *Angew. Chem. Int. Ed.* **2004**, 43, 550–556.
- 3 N. A. Paras; D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, 124, 7894–7895.
- 4 M. Johannsen, *Chem. Commun.* **1999**, 2233–2234.
- 5 H. Yamamoto, In *Lewis Acids in Organic Synthesis*, Wiley–VCH: Weinheim, **2000**.
- 6 N.A. Paras; D.W.A. MacMillan, *J. Am. Chem. Soc.* **2001**, 123, 4370–4371.
- 7 (a) A. Ishii; V.A. Soloshonok; K. Mikami, *J. Org. Chem.* **2000**, 65, 1597–1599; (b) N. Gathergood; W. Zhuang; K. A. Jørgensen, *J. Am. Chem. Soc.* **2000**, 122, 12517–12522; (c) Y. Yuan; X. Wang; W. Li; K. Ding, *J. Org. Chem.* **2004**, 69, 146–149; (d) W. Zhuang; N. Gathergood; R. G. Hazell; K.A. Jørgensen *J. Org. Chem.* **2001**, 66, 1009–1013; (e) A. Corma; H. García; A. Moussaïf; M. J. Sabater; R. Zniher; A. Redouane, *Chem. Commun.* **2002**, 1058–1059; (f) S. Saaby, P. Bayón, P. S. Aburel, K. A. Jørgensen, *J. Org. Chem.* **2002**, 67, 4352–4361.
- 8 (a) W. Zhuang, T. Hansen, K. A. Jørgensen, *Chem. Commun.* **2001**, 347–348; (b) J. Zhou, Y. Tang, *J. Am. Chem. Soc.* **2002**, 124, 9030–9031; (c) K. B. Jensen, J. Thorhauge, R. G. Hazell, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2001**, 40, 160–163; (d) M. Bandini, M. Fagioli, A. Melloni, A. Umani-Ronchi, *Tetrahedron Lett.* **2003**, 44, 5843–5846; (e) J. A. Austin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, 124, 1172–1173; (f) D. A. Evans, K. A. Scheidt, K. R. Fandrick, H. W. Lam, J. Wu, *J. Am. Chem. Soc.* **2003**, 125, 10780–10781; (g) M. Bandini, A. Melloni, S. Tommasi, A. Umani-Ronchi, *Helv. Chim. Acta*, **2003**, 86, 3753–3763.
- 9 D. W. C. MacMillan, K.A. Ahrendt, Patent, No.: US 6,515,137 B2.
- 10 M. Bandini, P. G. Cozzi, P. Melchiorre, A. Umani-Ronchi, *Angew. Chem. Int. Ed.* **2004**, 43, 84–87.

References and Notes to Section 1.3.1.3

- 1 R. M. Roberts, A. A. Khalaf, In *Friedel–Crafts Alkylation Chemistry. A Century of Discovery*, Marcel Dekker: New York, **1984**.

References and Notes to Section 1.3.1.4

- 1 (a) J. F. Normant, A. Alexakis, *Synthesis* **1981**, 841–870; (b) E. Negishi, T. Takahashi, *Synthesis* **1988**, 1–19.
- 2 M. T. Reetz, K. Sommer, *Eur. J. Org. Chem.* **2003**, 3485–3496.
- 3 (a) C. Jia, W. Lu, J. Oyamada, T. Kitamura, K. Matsuda, M. Irie, Y. Fujiwara, *J. Am. Chem. Soc.* **2000**, 122, 7252–7263; (b) C. Jia, D. Piao, J. Oyamada, W. Lu, T. Kitamura, Y. Fujiwara, *Science* **2000**, 287, 1992–1995; (c) C. Jia, D. Piao, T. Kitamura, Y. Fujiwara, *J. Org. Chem.* **2000**, 65, 7516–7522; (d) T. Tsuchimoto, T. Maeda, E. Shirakawa, Y. Kawakami, *Chem. Commun. (Cambridge, U. K.)* **2000**, 1573–1574; (e) G. Sartori, F. Bigi, A. Pastorio, C. Porta, A. Arienti, R. Maggi, N. Moretti, G. Gnappi, *Tetrahedron Lett.* **1995**, 36, 9177–9180.
- 4 K. Sommer, Dissertation, Ruhr-Universität Bochum, Germany, **2003**.
- 5 Gold(III)-catalyzed addition of oxygen nucleophiles to alkynes: (a) R. O. C. Norman, W. J. E. Parr, C. B. Thomas, *J. Chem. Soc., Perkin Trans. I* **1976**, 1983–1987; (b) Y. Fukuda, K. Utimoto, *J. Org. Chem.* **1991**, 56, 3729–3731; (c) Y. Fukuda, K. Utimoto, *Bull. Chem. Soc. Jpn.* **1991**, 64, 2013–2015; (d) Y. Fukuda, K. Utimoto, *Synthesis* **1991**, 975–978; (e) F. Gasparrini, M. Giovannoli, D. Misiti, G. Natile, G. Palmieri, L. Maresca, *J. Am. Chem. Soc.* **1993**, 115, 4401–4402; Nitrogen nucleophiles: (f) M. Deetlefs, H. G. Raubenheimer, M. W. Esterhuysen, *Catal. Today* **2002**, 72, 29–41; (g) A. Arcadi, S. D. Giuseppe, F. Marinelli, E. Rossi, *Adv. Synth. Catal.* **2001**, 343, 443–446; Gold(I)-catalyzed addition of oxygen nucleophiles to alkynes: (h) J. H. Teles, S. Brode, M. Chabanas, *Angew. Chem.* **1998**, 110, 1475–1478; *Angew. Chem. Int. Ed.* **1998**, 37, 1415–1418; (i) J. H. Teles, M. Schulz, BASF AG, WO-A 97/21648, **1997** [*Chem. Abstr.* **1997**, 127, 121499u]; (j) E. Mizushima, K. Sato, T. Hayashi, M. Tanaka, *Angew. Chem.* **2002**, 114, 4745–4747; *Angew. Chem. Int. Ed.* **2002**, 41, 4563–4565; Gold(III)-catalyzed C–C, C–O and C–N bond coupling reactions: (k) A. S. K. Hashmi, L. Schwarz, J.-H. Choi, T. M. Frost, *Angew. Chem. Int. Ed.* **2000**, 39, 2285–2288; (l) A. S. K. Hashmi, T. M. Frost, J. W. Bats, *Catal. Today* **2002**, 72, 19–27; (m) A. S. K. Hashmi, T. M. Frost, J. W. Bats, *Org. Lett.* **2001**, 3, 3769–3771; (n) A. S. K. Hashmi, T. M. Frost, J. W. Bats, *J. Am. Chem. Soc.* **2000**, 122, 11553–11554; (o) A. Hoffmann-Röder, N. Krause, *Org. Lett.* **2001**, 3, 2537–2538; (p) N. Asao, K. Takahashi, S. Lee, T. Kasahara, Y. Yamamoto, *J. Am. Chem. Soc.* **2002**, 124, 12650–12651; (q) S. Kobayashi, K. Kakumoto, M. Sugiura, *Org. Lett.* **2002**, 4, 1319–1322; (r) A. Arcadi, G. Bianchi, S. Di Giuseppe, F. Marinelli, *Green Chem.* **2003**, 5, 64–67; (s) Z. Shi, C. He, *J. Am. Chem. Soc.* **2004**, 126, 5964–5965; (t) J. J. Kennedy-Smith, S. T. Staben, F. D. Toste, *J. Am. Chem. Soc.* **2004**, 126, 4526–4527; (u) A. Arcadi, G. Bianchi, M. Chiarini, G. D’Anniballe, F. Marinelli, *Synlett* **2004**, 944–950; (v) C. Nieto-Oberhuber, M. P. Muñoz, E. Buñuel, C. Nevado, D. J. Cárdenas, A. M. Echavarren, *Angew. Chem.* **2004**, 116, 2456–2460; *Angew. Chem. Int. Ed.* **2004**, 43, 2402–2406; (w) V. Mamane, T. Gress, H. Krause, A. Fürstner, *J. Am. Chem. Soc.* **2004**, 126, 8654–8655; Recent reviews on gold catalysis: (x) G. Dyker, *Angew. Chem.* **2000**, 112, 4407–4409; *Angew. Chem. Int. Ed.* **2000**, 39, 4237–4239; (y) G. C. Bond, *Catal. Today* **2002**, 72, 5–9.
- 6 (a) M. S. Kharasch, H. S. Isbell, *J. Am. Chem. Soc.* **1931**, 53, 3053–3059; (b) K. S. Liddle, C. Parkin, *J. Chem. Soc., Chem. Commun.* **1972**, 26; (c) P. W. J. de Graaf, J. Boersma, G. J. M. van der Kerk, *J. Organomet. Chem.* **1976**, 105, 399–406; (d) Y. Fuchita, Y. Utsunomiya, M. Yasutake, *J. Chem. Soc., Dalton Trans.* **2001**, 2330–2334.
- 7 M. Preisenberger, A. Schier, H. Schmidbaur, *J. Chem. Soc., Dalton Trans.* **1999**, 1645–1650.
- 8 (a) A. Fürstner, V. Mamane, *J. Org. Chem.* **2002**, 67, 6264–6267; see also:

- (b) S. J. Pastine, S. W. Youn, D. Sames, *Org. Lett.* **2003**, 5, 1055–1058.
 9 Z. Shi, C. He, J. *Org. Chem.* **2004**, 69, 3669–3671.

References to Section 1.3.2.1

- 1 R. H. Crabtree, *Chem. Rev.* **1985**, 85, 245–269.
- 2 F. Kakiuchi, S. Murai, *Top. Organomet. Chem.* **1999**, 3, 47–79; F. Kakiuchi, N. Chatani, N. *Adv. Synth. Catal.* **2003**, 345, 1077–1101.
- 3 S. Murai, F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatani, *Nature* **1993**, 366, 529–531.
- 4 L. N. Lewis, J. F. Smith, *J. Am. Chem. Soc.* **1986**, 108, 2728–2735.
- 5 R. F. Jordan, Taylor, D. F. J. *Am. Chem. Soc.* **1989**, 111, 778–779; S. Rodewald, R. F. Jordan, *J. Am. Chem. Soc.* **1994**, 116, 4491–4492.
- 6 F. Kakiuchi, Y. Yamamoto, N. Chatani, S. Murai, *Chem Lett* **1995**, 681–682.
- 7 F. Kakiuchi, S. Murai, *Acc. Chem. Res.* **2002**, 35, 826–834.
- 8 F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatani, S. Murai, *Bull. Chem. Soc. Jpn.* **1995**, 68, 62–83; M. Sonoda, F. Kakiuchi, N. Chatani, M. Murai, *Bull. Chem. Soc. Jpn.* **1997**, 70, 3117–3128.
- 9 T. Matsubara, N. Koga, D. G. Musaev, K. Morokuma, *J. Am. Chem. Soc.* **1998**, 120, 12692–12693; T. Matsubara, N. Koga, D. G. Musaev, K. Morokuma, *Organometallics* **2000**, 19, 2318–2329.
- 10 C. P. Lenges, M. Brookhart, *J. Am. Chem. Soc.* **1999**, 121, 6616–6623.
- 11 P. W. R. Harris, P. D. Woodgate, *J. Organomet. Chem.* **1997**, 530, 211–223.
- 12 Y. Guari, S. Sabo-Etienne, B. Chaudret, *J. Am. Chem. Soc.* **1998**, 120, 4228–4229.
- 13 R. Grigg, V. Savic, *Tetrahedron Lett.* **1997**, 38, 5737–5740.
- 14 S. K. Gupta; W. P. Weber, *Macromolecules* **2002**, 35, 3369–3373.
- 15 M. Sonoda, F. Kakiuchi, A. Kamatani, N. Chatani, S. Murai, *Chem. Lett.* **1996**, 109–110; F. Kakiuchi, H. Ohtaki, M. Sonoda, N. Chatani, S. Murai, *Chem. Lett.* **2001**, 918–919.

- 16 F. Kakiuchi, T. Sato, K. Igi, N. Chatani, S. Murai, *Chem. Lett.* **2001**, 386–387.
- 17 R. Aufdenblatten, S. Diezi, A. Togni, *Monatsh. Chem.* **2000**, 131, 1345–1350.
- 18 P. W. R. Harris, C. E. F. Rickard, P. D. Woodgate, *J. Organomet. Chem.* **1999**, 589, 168–179.
- 19 T. M. Londergan, Y. You, M. E. Thompson, W. P. Weber, *Macromolecules* **1998**, 31, 2784–2788.
- 20 F. Kakiuchi, S. Murai, *Org. Synth.* **2003**, 80, 104–110.

References and Notes to Section 1.3.2.2

- 1 F. Kakiuchi, N. Chatani, *Adv. Synth. Catal.* **2003**, 345, 1077–1101.
- 2 E. J. Moore, W. R. Pretzer, T. J. O'Connell, J. Harris, L. LaBounty, L. Chou, S. S. Grimmer, *J. Am. Chem. Soc.* **1992**, 114, 5888.
- 3 N. Chatani, T. Fukuyama, F. Kakiuchi, S. Murai, *J. Am. Chem. Soc.* **1996**, 118, 493–494. N. Chatani, T. Fukuyama, H. Tatamidani, F. Kakiuchi, S. Murai, *J. Org. Chem.* **2000**, 65, 4039–4047.
- 4 T. Fukuyama, N. Chatani, J. Tatsumi, F. Kakiuchi, S. Murai, *J. Am. Chem. Soc.* **1998**, 120, 11522–11523.
- 5 N. Chatani, Y. Ie, F. Kakiuchi, S. Murai, *J. Org. Chem.* **1997**, 62, 2604–2610.
- 6 Y. Ie, N. Chatani, T. Ogo, D. R. Marshall, T. Fukuyama, F. Kakiuchi, S. Murai, *J. Org. Chem.* **2000**, 65, 1475–1488.
- 7 T. Asaumi, N. Chatani, T. Matsuo, F. Kakiuchi, S. Murai, *J. Org. Chem.* **2003**, 68, 7538–7340. T. Asaumi, T. Matsuo, T. Fukuyama, Y. Ie, F. Kakiuchi, N. Chatani, *J. Org. Chem.* **2004**, 69, 4433–4440.
- 8 N. Chatani, S. Yorimitsu, T. Asaumi, F. Kakiuchi, S. Murai, *J. Org. Chem.* **2002**, 67, 7557–7560.
- 9 Y. Ishii, N. Chatani, F. Kakiuchi, S. Murai, *Organometallics* **1997**, 16, 3615–3622.
- 10 J. W. Szewczyk, R. L. Zuckerman, R. G. Bergman, J. A. Ellman, *Angew. Chem. Int. Ed.* **2001**, 40, 216–219.
- 11 N. Chatani, T. Asaumi, S. Yorimitsu, T. Ikeda, F. Kakiuchi, S. Murai, *J. Am. Chem. Soc.* **2001**, 123, 10935–10941.

- 12 N. Chatani, T. Asaumi, T. Ikeda, S. Yorimitsu, Y. Ishii, F. Kakiuchi, S. Murai, *J. Am. Chem. Soc.* **2000**, *122*, 12882–12883.

References and Notes to Section 1.3.2.3

- 1 M. Lail, B. N. Arrowood, T. B. Gunnoe, *J. Am. Chem. Soc.* **2003**, *125*, 7506.
- 2 M. Lail, C. M. Bell, D. Conner, T. R. Cundari, T. B. Gunnoe, J. L. Petersen, *Organometallics* **2004**, *23*, 5007–5020.
- 3 K. A. Pittard, J. P. Lee, T. R. Cundari, T. B. Gunnoe, J. L. Petersen, *Organometallics* **2004**, *23*, 5514–5523.
- 4 B. N. Arrowood, M. Lail, T. B. Gunnoe, P. D. Boyle, *Organometallics* **2003**, *22*, 4692.
- 5 R. A. Periana, X. Y. Liu, G. Bhalla, *Chem. Commun.* **2002**, *24*, 3000.
- 6 T. Matsumoto, D. J. Taube, R. A. Periana, H. Taube, H. Yoshida, *J. Am. Chem. Soc.* **2000**, *122*, 7414.
- 7 T. Matsumoto, R. A. Periana, D. J. Taube, H. Yoshida, *J. Mol. Catal. A: Chemical* **2002**, *180*, 1.
- 8 J. Oxgaard, W. A. Goddard III, *J. Am. Chem. Soc.* **2004**, *126*, 442.
- 9 J. Oxgaard, R. P. Muller, W. A. Goddard III, R. A. Periana, *J. Am. Chem. Soc.* **2004**, *126*, 352.
- 10 I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009.
- 11 R. F. Heck, in *Comp. Org. Syn.*, Vol. 4 (Eds.: B. M. Trost, I. Fleming, M. F. Semmelhack), Pergamon Press, Oxford, **1999**, pp. 833.
- 12 J. K. Stille, *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508.
- 13 N. Miyauchi, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457.
- 14 E.-I. Negishi, L. Anastasia, *Chem. Rev.* **2003**, *103*, 1979.
- 15 J. Oxgaard, R. A. Periana, W. A. Goddard III, *J. Am. Chem. Soc.* **2004**, *126*, 11658–11665.
- 2 Moore, E. J.; Pretzer, W. R.; O'Connell, T. J.; Harris, J.; Labounty, L.; Chou, L.; Grimmer, S. S. *J. Am. Chem. Soc.* **1992**, *114*, 5888–5890.
- 3 Szewczyk, J. W.; Zuckerman, R. L.; Bergman, R. G.; Ellman, J. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 216–219.
- Chatani, N.; Fukuyama, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **1996**, *118*, 493–494.
- Fukuyama, T.; Chatani, N.; Tatsumi, J.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **1998**, *120*, 11522–11523.
- Chatani, N.; Fukuyama, T.; Tatamidani, H.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **2000**, *65*, 4039–4047.
- 4 Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 2685–2686.
- 5 Thalji, R. K.; Ahrendt, K. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 9692–9693.
- Jun, C. H.; Hong, J. B.; Kim, Y. H.; Chung, K. Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 3440–3442.
- Lim, Y. G.; Kang, J. B.; Kim, Y. H. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2201–2206.
- 6 Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 3202–3203.
- 7 Herrmann, W. A.; Kocher, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2163–2187.
- 8 Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 13964–13965.
- 9 Tan, K. L.; Vasudevan, A.; Bergman, R. G.; Ellman, J. A.; Souers, A. J. *Org. Lett.* **2003**, *5*, 2131–2134.
- 10 Wiedemann, S. H.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 1685–1687.
- 11 Lewis, J. C.; Wiedemann, S. H.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 35–38.
- 12 This notion is supported by the observation that, when the nitrogen lone pair and the reactive C–H bond are not proximal (as in the thermodynamically favored isomer of an acyclic formamidine), no alkylation takes place.
- 13 This prediction is born out by the observed zero-order dependence of the reaction on substrate concentration.
- 14 Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717–727.

References and Notes to Section 1.3.2.4

- 1 Jordan, R.; Taylor, D. *J. Am. Chem. Soc.* **1989**, *111*, 778–779.

- 15 Tan, K. L.; Park, S.; Ellman, J. A.; Bergman, R. G., submitted for publication.
- 16 Gant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, 50, 2297–2360.
- 17 Mori, A.; Sekiguchi, A.; Masui, K.; Shimada, T.; Horie, M.; Osakada, K.; Kawamoto, M.; Ikeda, T. *J. Am. Chem. Soc.* **2003**, 125, 1700–1701. Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2003**, 125, 5274–5275.
- 18 Wiedemann, S. H.; Lewis, J. C.; Bergman, R. G.; Ellman, J. A. manuscript in preparation.
- 19 $\text{PCy}_3 \cdot \text{HCl}$ is prepared by precipitation from a mixture of HCl and PCy_3 solutions in ether [9].
- Y. Fujiwara, *Bull. Chem. Soc. Jpn.* **2003**, 76, 1889–1895.
- 8 T. Mitsudome, T. Umetani, T. Mizugaki, K. Ebitani, K. Kaneda, *Catalyst Catalysis* **2004**, 46, 78–80.

References and Notes to Section 1.3.2.6

References and Notes to Section 1.3.2.5

- 1 (a) I. Moritani, Y. Fujiwara, *Tetrahedron Lett.* **1967**, 1119–1122. (b) I. Moritani, Y. Fujiwara, *Synthesis* **1973**, 524–533. (c) C. Jia, T. Kitamura, Y. Fujiwara, *Acc. Chem. Res.* **2001**, 34, 633–639. (d) Y. Fujiwara, *Palladium-Promoted Alkene–Arene Coupling via C–H Activation*, in: *Handbook of Organopalladium Chemistry for Organic Synthesis*, E.-i. Negishi (Ed.), John Wiley and Sons, 2002, pp. 2863–2871.
- 2 F. Kakiuchi, S. Murai, *Acc. Chem. Res.* **2002**, 35, 826–834.
- 3 (a) C. Jia, D. Piao, J. Oyamada, W. Lu, T. Kitamura, Y. Fujiwara, *Science* **2000**, 287, 1992–1995. (b) C. Jia, W. Lu, J. Oyamada, T. Kitamura, K. Matsuda, M. Irie, Y. Fujiwara, *J. Am. Chem. Soc.* **2000**, 122, 7252–7263. (c) C. Jia, D. Piao, T. Kitamura, Y. Fujiwara, *J. Org. Chem.* **2000**, 65, 7516–7522.
- 4 W. Lu, C. Jia, T. Kitamura, Y. Fujiwara, *Org. Lett.* **2000**, 2, 2927–2930.
- 5 Y. Fuchita, K. Hiraki, Y. Kamogawa, M. Suenaga, K. Tohogoh, Y. Fujiwara, *Bull. Chem. Soc. Jpn.* **1989**, 62, 1081–1085.
- 6 J. Oyamada, W. Lu, C. Jia, T. Kitamura, Y. Fujiwara, *Chem. Lett.* **2002**, 20–21.
- 7 (a) J. Oyamada, C. Jia, Y. Fujiwara, T. Kitamura, *Chem. Lett.* **2002**, 380–381. (b) T. Kitamura, K. Yamamoto, M. Kotani, J. Oyamada, C. Jia, Y. Fujiwara, *Bull. Chem. Soc. Jpn.* **2001**, 79, 1086–1092; (b) M. S. Stephan, A. J. J. M. Teunissen, G. K. M. Verzijl, J. G. de Vries, Johannes, *Angew. Chem. Int. Ed.* **1998**, 37, 662–664; (c) L. J. Goossen, J. Paetzold, *Synlet*, **2002**, 1721–1723.
- 2 (a) A. E. Shilov, G. B. Shul'pin, *Activation and Catalytic Reactions of Saturated Hydrocarbons in the Presence of Metal Complexes*, **2000**, Catalysis by Metal Complexes, Volume 21, B. R. James, P. W. N. M. van Leeuwen, Eds. Kluwer Academic Publishers; (b) F. Kakiuchi, N. Chatani, *Adv. Synth. Catal.* **2003**, 345, 1077–1101.
- 3 (a) I. Moritani, Y. Fujiwara, *Tetrahedron Lett.* **1967**, 1119–1122; (b) I. Moritani, Y. Fujiwara, *Synthesis* **1973**, 524–533; (c) C. Jia, T. Kitamura, Y. Fujiwara, *Acc. Chem. Res.* **2001**, 34, 633–639; (d) Y. Fujiwara, *Palladium-Promoted Alkene–Arene Coupling via C–H Activation*, in: *Handbook of Organopalladium Chemistry for Organic Synthesis*, E.-i. Negishi (Ed.) John Wiley and Sons, 2002, pp. 2863–2871; (e) F. Kakiuchi, S. Murai, *Acc. Chem. Res.* **2002**, 35, 826–834.
- 4 (a) Y. Fujiwara, I. Moritani, S. Danno, S. Teranishi, *J. Am. Chem. Soc.* **1969**, 91, 7166–7169 and references therein; (b) J. Tsuji, H. Nagashima, *Tetrahedron* **1984**, 40, 2699–702.
- 5 C. Jia, W. Lu, T. Kitamura, Y. Fujiwara, *Org. Lett.* **1999**, 1, 2097–2100.
- 6 A. C. Cope, R. W. Siekman, *J. Am. Chem. Soc.* **1965**, 87, 3272–3273; (b) V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev.* **2002**, 102, 1731–1769; (c) M. Pfeffer, *Rec. Trav. Chim. Pays-Bas* **1990**, 109, 567–76.
- 7 (a) H. Horino, N. Inoue, *J. Org. Chem.* **1981**, 46, 4416–4422; (b) S. J. Tremont,

- H. Ur Rahman, *J. Am. Chem. Soc.* **1984**, *106*, 5759–60.
- 8 M. D. K. Boele, G. P. F. van Strijdonck, A. H. M. de Vries, P. C. J. Kamer, J. G. de Vries, P. W. N. M. van Leeuwen, *J. Am. Chem. Soc.* **2002**, *124*, 1586–1587.
 - 9 C. Jia, D. Piao, J. Oyamada, W. Lu, T. Kitamura, Y. Fujiwara, *Science* **2000**, *287*, 1992–1995.
 - 10 (a) Z. Zhang, X. Lu, Z. Xu, Q. Zhang, X. Han, *Organometallics* **2001**, *20*, 3724–3728; (b) Z. Wang, Z. Zhang, X. Lu, *Organometallics* **2000**, *19*, 775–780.
 - 11 H. Grennberg, A. Gogoll, J.-E. Bäckvall, *Organometallics* **1993**, *12*, 1790–1793.
 - 12 (a) J.-E. Bäckvall, *Pure Appl. Chem.* **1992**, *64*, 429–437 and references therein
(b) P. Roffia, F. Conti, G. Gregorio, G. F. Pregaglia, R. Ugo, *J. Organomet. Chem.* **1973**, *391*, 391–394 and references therein.
 - 13 A. D. Ryabov, I. K. Sakodinskaya, A. K. Yatsimirsky, *J. Organomet. Chem.* **1991**, *406*, 309–321.
 - 14 (a) T. Yokota, M. Tani, S. Sakaguchi, Y. Ishii, *J. Am. Chem. Soc.* **2003**, *125*, 1476–1477; (b) M. Tani, S. Sakaguchi, Y. Ishii, *J. Org. Chem.* **2004**, *69*, 1221–1226.
 - 15 S. S. Stahl, *Angew. Chem. Int. Ed.* **2004**, *43*, 3400–3420.
 - 16 M. Dams, D. E. de Vos, S. Celen, P. A. Jacobs, *Angew. Chem. Int. Ed.* **2003**, *42*, 3512–3515.
 - 17 E. M. Ferreira, B. M. Stoltz, *J. Am. Chem. Soc.* **2003**, *125*, 9578–9579.
 - 18 H. Zhang, E. M. Ferreira, B. M. Stoltz, *Angew. Chem. Int. Ed.* **2004**, *43*, 6144–6148.
 - 19 S. Ma, S. Yu, *Tetrahedron Lett.* **2004**, *45*, 8419–8422.
 - 20 E. J. Hennessy, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 12084–12085.
 - 21 G. Karig, M.-T. Moon, N. Thasana, T. Gallagher, *Org. Lett.* **2002**, *4*, 3115–3118.
 - 22 C. Zhou, R. C. Larock, *J. Am. Chem. Soc.* **2004**, *126*, 2302–2303.
 - 23 A. D. Ryabov, *Chem. Rev.* **1990**, *90*, 403/424.

References to Section 1.3.3

- 1 A. Studer and M. Bossart *Radicals in Organic Synthesis* P. Renaud and M. P. Sibi Eds, Vol. II, pg 62, Wiley–VCH, **2001**.
- 2 Reviews: (a) F. Minisci, *Synthesis*, **1973**, *1*; (b) F. Minisci and O. Porta, *Advances in Heterocyclic Chemistry*, A. R. Katritzky Ed., Vol. 16, pg 123, Academic Press, **1974**; (c) F. Minisci, *Top. Curr. Chem.*, **1976**, 621; (d) F. Minisci and O. Porta, *Zh. Yses. Khim.. D-Va* **1979**, *24*, 121; (e) F. Minisci and O. Porta, *La Chimica e l'Industria*, **1980**, *62*, 769–775; (f) F. Minisci, *Fundamental Research in Homogeneous Catalysis*, M. Graziani Ed., Vol 4, pg 173, Plenum, **1984**; (g) F. Minisci, *Substituent Effects in radical Chemistry* H. G. Viehe Ed., pg 391, Reidel, **1986**; (h) F. Minisci and E. Vismara, *Organic Synthesis: Modern Trends*, O. Chizhov Ed., pg 229, Blackwell Sci. Publ., **1987**; (i) F. Minisci, F. Fontana and E. Vismara, *Heterocycles*, **1989**, *28*, 489; (l) F. Minisci, F. Fontana and E. Vismara, *J. Heterocyclic Chem.*, **1990**, *27*, 79.
- 3 (a) A. Citterio, F. Minisci, O. Porta and G. Sesana *J. Am. Chem. Soc.*, **1977**, *99*, 7960; (b) F. Recupero, A. Bravo, H. R. Bjorsvik, F. Fontana, F. Minisci and M. Piredda, *J. Chem. Soc. Perkin Trans II*, **1997**, 2399.
- 4 A. Clerici, N. Pastori and O. Porta, *Tetrahedron Lett.*, **2004**, *45*, 1825.
- 5 F. Minisci, F. Recupero, A. Cecchetto, C. Punta, C. Gambarotti, F. Fontana and G. F. Pedulli, *J. Heterocyclic Chem.*, **2003**, *40*, 325.
- 6 F. Minisci, A. Citterio, E. Vismara e C. Giordano, *Tetrahedron*, **1985**, *41*, 4157.
- 7 C. Giordano, F. Minisci, E. Vismara and S. Levi, *J. Org. Chem.*, **1986**, *51*, 536.
- 8 F. Minisci, E. Vismara, F. Fontana, G. Morini, M. Serravalle and C. Giordano, *J. Org. Chem.*, **1986**, *51*, 4411.
- 9 T. Caronna, A. Citterio, T. Crolla and F. Minisci, *J. Chem. Soc. Perkin Trans II*, **1977**, 865.

- 10 F. Minisci, A. Citterio, M. Perchinunno and F. Bertini, *Gazz. Chim. Ital.*, **1975**, *105*, 1083.
- 11 F. Fontana, F. Minisci, M. C. Nogueira Barbosa and E. Vismara, *Tetrahedron*, **1990**, *46*, 2525.
- 12 F. Fontana, F. Minisci, M. C. Nogueira Barbosa and E. Vismara, *J. Org. Chem.*, **1991**, *56*, 2866.
- 13 F. Coppa, F. Fontana, E. Lazzarini and F. Minisci, *Heterocycles*, **1993**, *36*, 2687.
- 14 F. Coppa, F. Fontana, E. Lazzarini, F. Minisci and G. Pianese, *Tetrahedron Lett.*, **1992**, *33*, 3057.
- 15 F. Minisci, O. Porta, F. Recupero, C. Punta, C. Gambarotti, B. Pruna, M. Pierini and F. Fontana, *Synlett*, **2004**, 874–876.
- 16 E. Vismara, A. Donna, F. Minisci, A. Naggi, N. Pastori and G. Torri, *J. Org. Chem.*, **1993**, *58*, 959.
- 17 F. Minisci, F. Fontana and E. Vismara, *Free Radicals in Synthesis and Biology* F. Minisci Ed., Kluwer, Dordrecht, **1989**, p. 53.
- 18 F. Antonietti, A. Mele, F. Minisci, C. Punta, F. Recupero and F. Fontana, *J. Fluorine Chem.*, **2004**, *125*, 205.
- 9 D. A. Culkin, J. F. Hartwig, *Acc. Chem. Res.* **2003**, *36*, 234–245.
- 10 Y. Kawamura, T. Satoh, M. Miura, M. Nomura, *Chem. Lett.* **1998**, 931–932.
- 11 A. R. Muci, S. L. Buchwald, *Top. Curr. Chem.* **2002**, *219*, 131–209.
- 12 R. B. Bedford, S. J. Coles, M. B. Hursthouse, M. E. Limmert, *Angew. Chem. Int. Ed.* **2003**, *42*, 112–114.
- 13 R. B. Bedford, M. E. Limmert, *J. Org. Chem.* **2003**, *68*, 8669–8682.
- 14 S. Oi, S. Watanabe, S. Fukita, Y. Inoue, *Tetrahedron Lett.* **2003**, *44*, 8665–8668.
- 15 T. Satoh, Y. Kametani, Y. Terao, M. Miura, M. Nomura *Tetrahedron Lett.* **1999**, *40*, 5345–5348.
- 16 Y. Kametani, T. Satoh, M. Miura, M. Nomura, *Tetrahedron Lett.* **2000**, *41*, 2655–2658.
- 17 S. Oi, Y. Ogino, S. Fukita, Y. Inoue, *Org. Lett.* **2002**, *4*, 1873–1785.
- 18 S. Oi, S. Fukita, N. Hirata, N. Watanuki, S. Miyano, Y. Inoue, *Org. Lett.* **2001**, *3*, 2579–2581.
- 19 B. Sezen, D. Sames, *J. Am. Chem. Soc.* **2003**, *125*, 10580–10585.
- 20 F. Kakiuchi, S. Kan, K. Igi, N. Chatani, S. Murai, *J. Am. Chem. Soc.* **2003**, *125*, 1698–1699.
- 21 S. Oi, S. Fukita, Y. Inoue, *Chem. Commun.* **1998**, 2439–2440.

References to Section 1.4.1.1

- 1 A. de Meijere, F. Diederich (Eds) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd edn, Wiley–VCH, Weinheim, **2004**.
- 2 J. Tsuji, *Palladium Reagents and Catalysts*, 2nd edn, Wiley, Chichester, **2004**.
- 3 J. Hassan, M. Sévignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359–1469.
- 4 M. Miura, M. Nomura, *Top. Curr. Chem.* **2002**, *219*, 211–241.
- 5 T. Satoh, Y. Kawamura, M. Miura, M. Nomura, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1740–1742.
- 6 T. Satoh, J. Inoh, Y. Kawamura, Y. Kawamura, M. Miura, M. Nomura, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2239–2246.
- 7 G. Dyker, *Chem. Ber./Recueil* **1997**, *130*, 1567–1578.
- 8 Y. Kawamura, T. Satoh, M. Miura, M. Nomura, *Chem. Lett.* **1999**, 961.

References to Section 1.4.1.2

- 1 M. Miura, M. Nomura, *Top. Curr. Chem.* **2002**, *219*, 211–241.
- 2 J. Hassan, M. Sévignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359–1469.
- 3 S. Pivsa-Art, T. Satoh, Y. Kawamura, M. Miura, M. Nomura, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467–473.
- 4 J. F. D. Chabert, L. Joucla, E. David, M. Lemaire, *Tetrahedron* **2004**, *60*, 3221.
- 5 Y. Akita, Y. Itagaki, S. Takizawa, A. Ohta, *Chem. Pharm. Bull.* **1989**, *37*, 1477–1480.
- 6 Y. Aoyagi, A. Inoue, I. Koizumi, R. Hashimoto, K. Tokunaga, K. Gohma, J. Komatsu, K. Sekine, A. Miyafuji, J. Kunoh, R. Honma, Y. Akita, A. Ohta, *Heterocycles* **1992**, *33*, 257–272.

- 7 B. Sezen, D. Sames, *J. Am. Chem. Soc.* **2003**, *125*, 5274–5275.
- 8 B. Sezen, D. Sames, *J. Am. Chem. Soc.* **2003**, *125*, 10580–10585.
- 9 C.-H. Park, V. Ryabova, I. V. Seregin, A. W. Sromek, V. Gevorgyan, *Org. Lett.* **2004**, *6*, 1159–1162.
- 10 A. Ohta, Y. Akita, T. Ohkuwa, M. Chiba, R. Fukunaga, A. Miyafuji, T. Nakata, N. Tani, Y. Aoyagi, *Heterocycles*, **1990**, *31*, 1951–1958.
- 11 M. S. McClure, B. Glover, E. McSorley, A. Millar, M. H. Osterhout, F. Roschanner, *Org. Lett.* **2001**, *3*, 1677–1680.
- 12 B. Glover, K. A. Harvey, B. Liu, M. J. Sharp, M. F. Tymoschenko, *Org. Lett.* **2003**, *5*, 301.
- 13 K. Masui, A. Mori, K. Okano, K. Takamura, M. Kinoshita, T. Ikeda, *Org. Lett.* **2004**, *6*, 2011–2014.
- 14 J. Hassan, C. Gozzi, E. Schulz, M. Lemaire, *J. Organomet. Chem.* **2003**, *687*, 280–283.
- 15 T. Okazawa, T. Satoh, M. Miura, M. Nomura, *J. Am. Chem. Soc.* **2002**, *124*, 5286–5287.
- 16 A. Yokoorji, T. Satoh, M. Miura, M. Nomura, *Tetrahedron* **2004**, *60*, 6757–6763.
- 17 M. Sévignon, J. Papillon, E. Schulz, M. Lemaire, *Tetrahedron Lett.* **1999**, *40*, 5873–5876.
- 18 *Comprehensive Heterocyclic Chemistry*, vols. 5 and 6 (Ed.: K. T. Potts), Pergamon Press, Oxford, **1984**.
- 19 J. C. Lewis, S. H. Wiedemann, R. G. Bergman, J. A. Ellman, *Org. Lett.* **2004**, *6*, 35–38.
- 20 W. Li, D. P. Nelson, M. S. Jensen, R. S. Hoerrner, G. J. Javadi, D. Cai, R. D. Larsen, *Org. Lett.* **2003**, *5*, 4835–4837.
- 21 B. Sezen, D. Sames, *Org. Lett.* **2003**, *5*, 3607–3610.
- 22 A. Yokoorji, T. Okazawa, T. Satoh, M. Miura, M. Nomura, *Tetrahedron* **2003**, *69*, 5685–5689.
- 23 A. Mori, A. Sekiguchi, K. Masui, T. Shimada, M. Horie, K. Osakada, M. Kawamoto, T. Ikeda, *J. Am. Chem. Soc.* **2003**, *125*, 1700–1701.
- 24 Y. Kondo, T. Komine, T. Sakamoto, *Org. Lett.* **2000**, *2*, 3111–3113.

References and Notes to Section 1.4.1.3

- 1 (a) C. Janiak, H. Schumann, *Adv. Organomet. Chem.* **1991**, *33*, 291–393; (b) J. Okuda, *Topics Curr. Chem.* **1991**, *160*, 97–145; (c) C. Janiak, R. Weimann, F. Görlitz, *Organometallics* **1997**, *16*, 4933–4936; (d) M. Bond, R. Colton, D. A. Fiedler, L. D. Field, D. Leslie, T. He, P. A. Humphrey, C. M. Lindall, F. Marken, A. F. Masters, H. Schumann, K. Suehring, V. Tedesco, *Organometallics* **1997**, *16*, 2787–2797; (e) D. Matt, M. Huhn, M. Bonnet, I. Tkatchenko, U. Englert, W. Kläul, *Inorg. Chem.* **1995**, *34*, 1288–1291; (f) S. Barry, A. Kucht, H. Kucht, M. D. Rausch, *J. Organomet. Chem.* **1995**, *489*, 195–199; (g) C. Ruble, H. A. Latham, G. C. Fu, *J. Am. Chem. Soc.* **1997**, *119*, 1492–1493; (h) A. M. Bond, R. Colton, D. A. Fiedler, L. D. Field, T. He, P. A. Humphrey, C. M. Lindall, F. Marken, A. F. Masters, H. Schumann, K. Suehring, V. Tedesco, *Organometallics* **1997**, *16*, 2787–2797; (i) H. Schumann, A. Lentz, R. Weimann, J. Pickardt, *Angew. Chem.* **1994**, *106*, 1827–1828, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1731–1732; (j) W. M. Harrison, C. Saadeh, S. B. Colbran, D. C. Craig, *J. Chem. Soc., Dalton Trans.* **1997**, 3785–3792.
- 2 (a) C. Adachi, T. Tsuji and S. Saito, *Appl. Phys. Lett.* **1990**, *56*, 799–801; (b) Y. Ohmori, Y. Hironaka, M. Yoshida, N. Tada, A. Fujii, K. Yoshino, *Synth. Metal* **1997**, *85*, 1241–1242.
- 3 (a) W. Broser, P. Siegle and H. Kurreck, *Chem. Ber.* **1968**, *101*, 69–83; (b) L. D. Field, K. M. Ho, C. M. Lindall, A. F. Masters, A. G. Webb, *Aust. J. Chem.* **1990**, *43*, 281–291; (c) T. R. Jack, C. J. May, J. Powell, *J. Am. Chem. Soc.* **1977**, *99*, 4707–4716; (d) H. Schumann, H. Kucht, A. Kucht, *Z. Naturforsch.* **1992**, *47b*, 1281–1289; (e) R. H. Lowack, K. P. C. Vollhardt, *J. Organomet. Chem.* **1994**, *476*, 25–32.
- 4 M. Miura, S. Pivsa-Art, G. Dyker, J. Heiermann, T. Satoh, M. Nomura, *Chem. Commun.* **1998**, 1889–1890.
- 5 G. Dyker, J. Heiermann, M. Miura, J.-I. Inoh, S. Pivsa-Art, T. Satoh,

- M. Nomura, *Chem. Eur. J.* **2000**, *6*, 3426–3433.
- 6 G. Dyker, J. Heiermann, M. Miura, *Adv. Synth. Catal.* **2003**, *345*, 1127–1132.
- 7 (a) A. F. Littke, G. C. Fu., *J. Org. Chem.* **1999**, *64*, 10–11; (b) G. Mann, C. Incarvito, A. L. Rheingold, J. F. Hartwig, *J. Am. Chem. Soc.* **1999**, *121*, 3224–3225.
- 8 W. A. Herrmann, C. Brossmer, C.-P. Reisinger, T. H. Riermeier, K. Öffe, M. Beller, *Chem. Eur. J.* **1997**, *3*, 1357–1364, and references cited therein.
- 9 (a) N. A. Beare, J. F. Hartwig, *J. Org. Chem.* **2002**, *67*, 541–555; (b) M. Jørgensen, S. Lee, X. Liu, J. P. Wolkowski, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 12557–12565; (c) D. A. Culkin, J. F. Hartwig, *Acc. Chem. Res.* **2003**, *36*, 234–245, and references cited therein.
- 10 G. Dyker, S. Borowski, J. Heiermann, J. Körning, K. Opwis, G. Henkel, M. Köckerling, *J. Organomet. Chem.* **2000**, *606*, 108–111.
- 5 G. Bringmann, J. R. Jansen, H. Reuscher, M. Rubenacker, K. Peters and H. G. von Schnering, *Tetrahedron Lett.*, **1990**, *31*, 643. See also: G. Bringmann, R. Walter and R. Weirich, *Angew. Chem. Int. Ed.*, **1990**, *29*, 977.
- 6 G. Bringmann, T. Pabst, P. Henschel, J. Kraus, K. Peters, E.-M. Peters, D. S. Rycroft and J. D. Connolly, *J. m. Chem. Soc.*, **2000**, *122*, 9127.
- 7 D. E. Ames and A. Opalko, *Synthesis*, **1983**, 235.
- 8 T. Iwaki, A. Yasuhara and T. Sakamoto, *J. Chem. Soc., Perkin Trans. 1*, **1999**, 1505.
- 9 D. E. Ames and D. Bull, *Tetrahedron*, **1982**, *38*, 383.
- 10 A. R. Katritzky, C. W. Rees, and E. F. Scriven (Eds) *Comprehensive Heterocyclic Chemistry II*, Pergamon, Oxford, 1996.
- 11 For a recent review on the isolation and synthesis of biologically active carbazoles see: H.-J. Knölker and K. R. Reddy, *Chem. Rev.* **2002**, *102*, 4303
- 12 For examples of this oxidative coupling method and leading references, see Ref. [11].
- 13 R. B. Bedford and C. S. J. Cazin, *Chem. Commun.*, **2002**, 2310.
- 14 R. B. Bedford, *Chem. Commun.*, **2003**, 1787.
- 15 B. Martín-Matute, C. Mateo, D. J. Cárenas and A. M. Echavarren, *Chem. Eur. J.*, **2001**, *7*, 2341.
- 16 R. B. Bedford and M. Betham, unpublished data
- 17 Originally isolated from the roots of *Clausina excavate*: T.S. Wu, S. C. Huang, P. L. Wu, C. C. Kuoh, *Phytochemistry*, **1999**, *52*, 523.
- 18 M. R. Netherton and G. C. Fu, *Org. Lett.*, **2001**, *3*, 4295.

References and Notes to Section 1.4.2.1

- 1 This method is also applicable to the synthesis of carbocyclic compounds, see: (a) J. E. Rice and Z.-W. Cai, *Tetrahedron Lett.*, **1992**, *33*, 1675; (b) J. E. Rice, Z.-W. Chen, *J. Org. Chem.*, **1993**, *58*, 1415; (c) B. E. Gómez-Lor, O. de Frutos and A. M. Echavarren, *Chem. Commun.*, **1999**, 2431; (d) J. E. Rice, Z.-W. Cai, Z.-M. He and E. J. LaVoie, *J. Org. Chem.*, **1995**, *60*, 8101; (e) J. J. Gonzáles, N. García, B. Gómez-Lor and A. M. Echavarren, *J. Org. Chem.*, **1997**, *62*, 1286; (f) O. de Frutos, B. Gómez-Lor, T. Granier, M. Á. Monge, E. Gutiérrez-Puebla and A. M. Echavarren, *Angew. Chem. Int. Ed.*, **1999**, *38*, 205; (g) L. Wang and P. B. Shevlin, *Tetrahedron Lett.*, **2000**, *41*, 285.
- 2 D. E. Ames and A. Opalko, *Tetrahedron*, **1984**, *40*, 1919.
- 3 T. Kuroda and F. Suzuki, *Tetrahedron Lett.*, **1991**, *47*, 6915.
- 4 P. P. Deshpande and O. R. Martin, *Tetrahedron Lett.*, **1990**, *44*, 6313.

References to Section 1.4.2.2

- 1 M. Catellani, *Synlett* and references cited therein **2003**, 298–313.
- 2 M. Catellani, G.P. Chiusoli, *J. Organomet. Chem.* **1985**, *286*, C13–C16.
- 3 M. Catellani, E. Motti, *New J. Chem.* **1998**, 759–761.

- 4 M. Catellani, E. Motti, M. Minari, *J. Chem. Soc., Chem. Commun.* **2000**, 157–158.
- 5 M. Catellani, F. Frignani, A. Rangoni, *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 119–122.
- 6 E. Motti, A. Mignozzi, M. Catellani, *J. Mol. Catal. A: Chem.* **2003**, 204–205, 115–124.
- 7 F. Faccini, E. Motti, M. Catellani, *J. Am. Chem. Soc.* **2004**, 126, 78–79 and unpublished results.
- 8 M. Lautens, J.-F. Paquin, S. Piguel, *J. Org. Chem.* **2002**, 67, 3972–3974.
- 9 M. Catellani, E. Motti, S. Baratta, *Org. Lett.* **2001**, 3, 3611–3614.
- 10 R. Ferraccioli, D. Carenzi, O. Rombolà, M. Catellani, *Org. Lett.* **2004**, 6, 4759–4762.
- 6 D. Mirk, B. Wibbeling, R. Fröhlich, S. R. Waldvogel, *Synlett* **2004**, 1970–1975.
- 7 B. Kramer, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2004**, 43, 2446–2449.
- 8 L. Czollner, W. Frantsits, B. Küenburg, U. Hedenig, J. Fröhlich, U. Jordis, *Tetrahedron Lett.* **1998**, 39, 2087–2088.
- 9 N. Boden, R. J. Bushby, Z. Lu, G. Headdock, *Tetrahedron Lett.* **2000**, 41, 10117–10120.
- 10 N. Naarmann, M. Hanack, R. Mattmer, *Synthesis* **1994**, 477–478.
- 11 G. Pohnert, *J. Prakt. Chem.* **2000**, 342, 731–734.
- 12 Y. Kita, M. Arisawa, M. Gyoten, M. Nakajima, R. Hamada, H. Tohma, T. Takada, *J. Org. Chem.* **1998**, 63, 6625–6633; Y. Kita, T. Takada, M. Gyoten, H. Tohma, M. H. Zenk, J. Eichhorn, *J. Org. Chem.* **1996**, 61, 5857–5864.
- 13 R. Olivera, R. San Martin, S. Pascual, M. Herrero, E. Dominguez, *Tetrahedron Lett.* **1999**, 40, 3479–3480.
- 14 B. Kramer, A. Averhoff, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2002**, 41, 2981–2982.
- 15 B. Kramer, R. Fröhlich, S. R. Waldvogel, *Eur. J. Org. Chem.* **2003**, 3549–3554.
- 16 B. Kramer, R. Fröhlich, K. Bergander, S. R. Waldvogel, *Synthesis* **2003**, 91–96.
- 17 D. Mirk, O. Kataeva, R. Fröhlich, S. R. Waldvogel, *Synthesis* **2003**, 2410–2414.
- 18 S. R. Waldvogel, *Synlett* **2002**, 622–624.
- 19 S. R. Waldvogel, E. Aits, C. Holst, R. Fröhlich, *Chem. Commun.* **2002**, 1278–1279.
- 20 S. R. Waldvogel, R. Fröhlich, C. A. Schalley, *Angew. Chem. Int. Ed.* **2000**, 39, 2472–2475.
- 1 G. Lessene, K. S. Feldman in *Modern Arene Chemistry*, Ed. D. Astruc, pages 479–538, Wiley–VCH, Weinheim, **2002**.
- 2 H.-J. Deuben, P. Frederiksen, T. Bjørnholm, K. Bechgaard, *Org. Prep. Proc. Int.* **1996**, 52, 484–486.
- 3 R. B. Herbert, E. E. Kattah, A. J. Murtagh, P. W. Sheldrake, *Tetrahedron Lett.* **1995**, 36, 5649–5650.
- 4 Y. Kita, M. Gyoten, M. Ohtsubo, H. Tohma, T. Takada, *Chem. Commun.* **1996**, 1481–1482; T. Takada, M. Arisawa, M. Gyoten, R. Hamada, H. Tohma, Y. Kita, *J. Org. Chem.* **1998**, 63, 7698–7706; H. Tohma, H. Morioka, S. Takizawa, M. Arisawa, Y. Kita, *Tetrahedron* **2001**, 57, 345–352; H. Tohma, M. Iwata, T. Maegawa, Y. Kita, *Tetrahedron Lett.* **2002**, 43, 9241–9244.
- 5 D. Mirk, A. Willner, R. Fröhlich, S. R. Waldvogel, *Adv. Synth. Catal.* **2004**, 346, 675–681.

References and Notes to Section 1.4.3

substrates. The combination of carbopalladation (Scheme 2) with other reaction steps into domino processes has further increased the preparative utility of this reaction.

The term “Heck reaction” is associated with such a huge variety of transformations that it is impossible to cover them all within the scope of this chapter. We therefore restricted ourselves to giving an outline of the reaction principle and discussing a number of illustrative developments in this exciting field of research. For a more comprehensive overview, we recommend recent review articles [6–8].

2.1.2

Mechanism

Because the catalytic Heck olefination evolved from stoichiometric organometallic transformations, its key elemental steps are relatively well-understood (Scheme 2) [9], although many mechanistic details are still unclear. The widely accepted mechanism of the Heck reaction starts with an oxidative addition of the organic halide **1** to a coordinatively unsaturated Pd(0) complex **a**, generated in situ from Pd(0) precursors or Pd(II) salts, yielding the σ -arylpalladium(II) complex **b** [10]. As a result of this reaction step, the electrophilicity of the Pd increases, favoring precoordination of the olefin (intermediate **c**). Insertion of the olefin **2** into the Pd–C bond of **c** results in the formation of the σ -alkylpalladium(II) complex **d**. Because β -hydride elimination requires at least one β -hydrogen in synperiplanar orientation relative to the halopalladium residue, elimination towards the original position of the C–C double bond can only proceed after an internal rotation around this bond, giving rise to the hydridopalladium olefin complex **e**. In this case, no new chiral center is formed in the product molecule. If, however, β -hydride elimination is forced in a different direction (intermediate **e'**), the stereogenic carbon atom created into the insertion step will be retained, and enantioselective reactions become possible (Section 2.1.3.4). Dissociation of the product olefins **3** or **3a** leads to the formation of the hydridopalladium species **f**. This can finally be converted back into the catalytically active Pd(0) complex **a** by reductive elimination of HX with the help of a base.

These fundamental steps of the catalytic cycle have been confirmed by stoichiometric reactions starting from isolated stable complexes, and by DFT calculations [11]. Although many aspects of the Heck olefination can be rationalized by this “textbook mechanism”, it provides no explanation of the pronounced influence that counter-ions of Pd(II) pre-catalysts or added salts have on catalytic activity [12]. This led Amatore and Jutand to propose a slightly different reaction mechanism [13]. They revealed that the preformation of the catalytically active species from Pd(II) salts does not lead to neutral Pd(0)L₂ species **a**; instead, three-coordinate anionic Pd(0)-complexes **g** are formed (Scheme 3, top). They also observed that on the addition of aryl iodides **1a** to such an intermediate **g**, a new species forms quantitatively within seconds and the solution remains free of iodide and acetate anions. It may then take several minutes before the expected stable, four-

2.1.3

Scope and Limitations

2.1.3.1 Substrates

In the Heck reaction, a vinylic hydrogen is replaced by an organic fragment, usually an alkenyl, aryl, allyl, or benzyl group, but there are also examples of analogous olefinations of alkoxy carbonylmethyl, alkynyl, silyl, and even some alkyl groups. Both intra- and intermolecular Heck reactions are known. The regioselectivity of intramolecular reactions is largely controlled by entropic factors, so the *exo-trig* products are formed preferentially. In intermolecular reactions, the olefin reacts preferentially at the sterically less crowded position, the polarization of the olefin playing a minor role [16]. Selected examples are shown in Fig. 1.

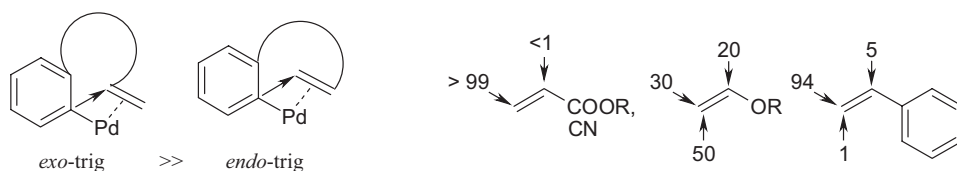
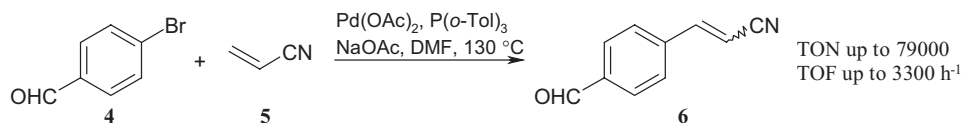


Figure 1. Regiochemical outcomes of the Heck reaction.

Mono- and 1,1-disubstituted olefins are the most reactive, but even tetrasubstituted alkenes have been used [17]. Because double-bond isomerization is a common side-reaction, olefins with a non-isomerizable bond are usually used.

2.1.3.2 Heck Reactions of Aryl Bromides and Iodides

The most widely used version of the Heck reaction is the coupling of aryl bromides or iodides with activated olefins such as styrene or acrylic acid derivatives, using conditions first described by Spencer [18]. The catalysts are generated in situ by combining $\text{Pd}(\text{OAc})_2$ with two to four equivalents of triphenyl- or tri-*o*-tolylphosphine. Triethylamine, K_2CO_3 , NaHCO_3 , or NaOAc are often used as the base.

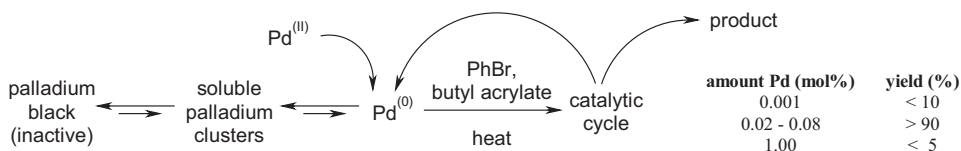


Scheme 4. Typical example of a Heck reaction following Spencer's improved procedure.

The most effective solvents for this reaction are polar aprotic solvents such as acetonitrile, DMF, NMP, or DMSO. Addition of halide salts such as tetra-*n*-butylammonium bromide strongly facilitates the reaction and enables the conversion of aryl iodides and activated bromides even in the absence of phosphines (Jeffery conditions) [19]. Under these conditions the presence of water was sometimes

found to be beneficial and there are even examples for Heck olefinations in aqueous solutions [20].

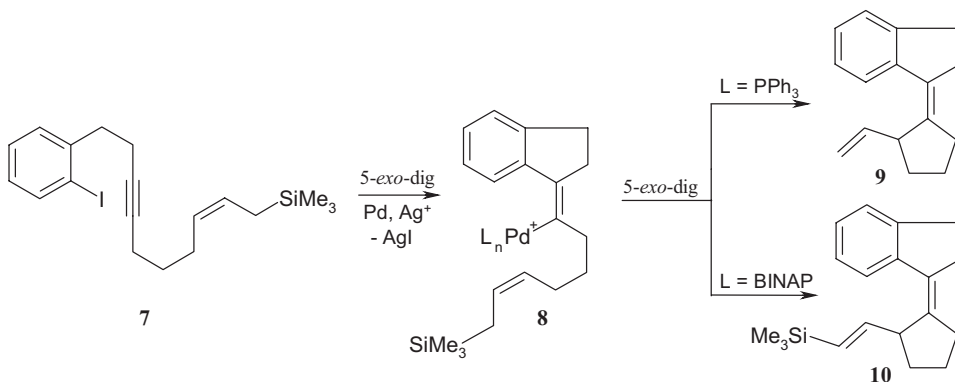
Because aryl phosphines are not only costly but can also act as aryl sources themselves, giving rise to unwanted byproducts, there has been steady interest in extending ligand-free Heck reactions to aryl bromides and aryl chlorides. Reetz and de Vries recently found that these can be performed with high efficiency using stabilized colloidal Pd catalysts [21]. If the palladium is kept at a low concentration between 0.01 and 0.1 mol%, precipitation of the Pd(0) is avoided and the colloids serve as a reservoir for the catalytically active species (Scheme 5). This economically attractive method has been successfully applied on an industrial scale by DSM [22].



Scheme 5. Heck reaction using colloidal palladium as catalyst.

2.1.3.3 Domino Reactions Involving Carbometallation Steps

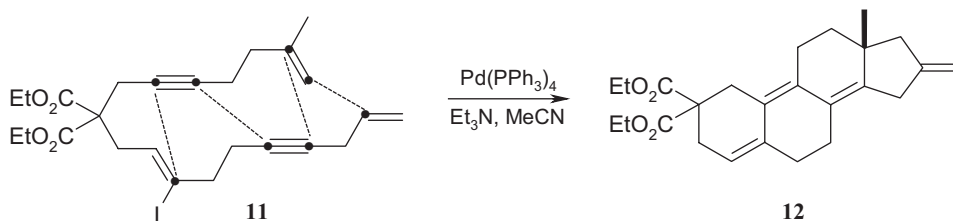
For domino Heck reactions the initial carbometallation step must lead to intermediates that do not readily undergo β -hydride elimination and can thus serve as starting points for additional Pd-mediated transformations [7]. Such processes, as exemplified in Scheme 6, have been used extensively by de Meijere, Grigg, Overman and others for assembly of complex carbon skeletons.



Scheme 6. Allylsilane-terminated cascade Heck reaction by Tietze et al.

In Tietze's example shown in Scheme 6 the palladium is eliminated away from the tertiary carbon center formed after two cyclization steps. Both the silane **10** and the desilylated product **9** are accessible, depending on the ligand employed [23].

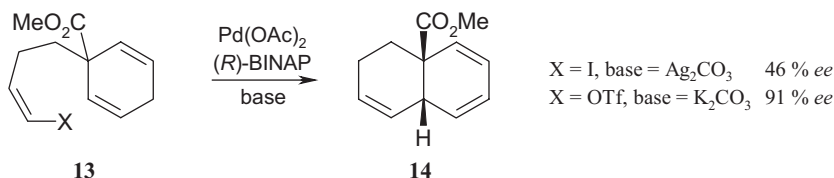
The name “zipper reactions” has been coined for cascade reactions in which a whole series of carbometalations proceed in a single reaction step [24]. In the example by Negishi shown in Scheme 7, palladium initially inserts into the vinylic carbon–iodine bond, then progresses along a line of multiple bonds, literally zipping the two chains of the substrate together to form the fused steroidal ring system **12**.



Scheme 7. Cascade Heck reaction.

2.1.3.4 Enantioselective Heck Reactions

In intramolecular Heck reactions, chiral centers can be generated by differentiation of either two enantiotopic leaving groups or two double bonds, or by double-bond migration. In the classical synthesis of a decalin ring system **14** (Scheme 8), two stereocenters were generated with high selectivity using the chiral ligand (*R*)-binaphthylidiphenylphosphine (BINAP) [25].

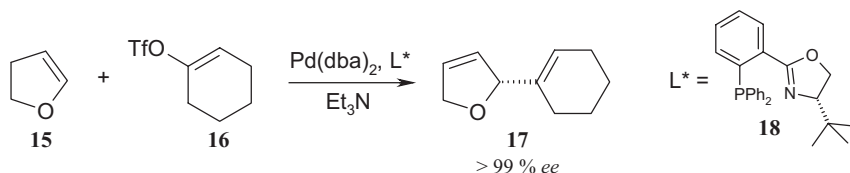


Scheme 8. Two stereocenters generated in an intramolecular Heck reaction.

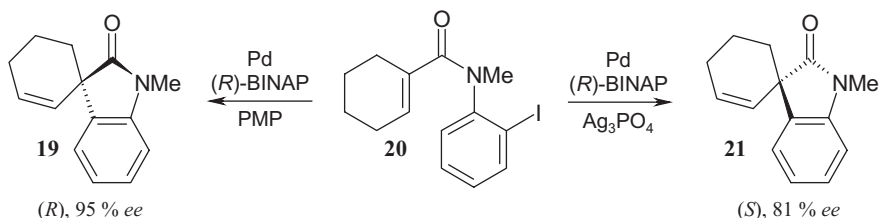
In this example, significant chiral induction can only be realized if silver salts are added to trap the iodide ions, and thus a chelating coordination mode of the chiral bidentate ligand is facilitated during coordination of the olefin (Scheme 2, cationic pathway). Even better results are obtained from substrates with non-coordinating leaving groups such as vinyl triflates.

These “cationic” conditions are also used for intermolecular Heck olefinations in which the chiral centers are generated via double-bond migration. The synthesis of 2-aryl-2,3-dihydrofurans **17** is a good example (Scheme 9) [26].

A cationic pathway is not compulsory for achieving high enantioselectivity, however – there are also examples in which conditions facilitating the neutral pathway (Scheme 2) are most effective. Interestingly, in an intramolecular Heck coupling performed by Overman et al., both enantiomers of spirocycles could be selectively generated using the same BINAP ligand (Scheme 10), depending on whether silver salts were used to sequester iodide (cationic pathway), or a tertiary amine was employed as an HI scavenger (neutral pathway) [27].



Scheme 9. Enantioselective intermolecular Heck reaction.

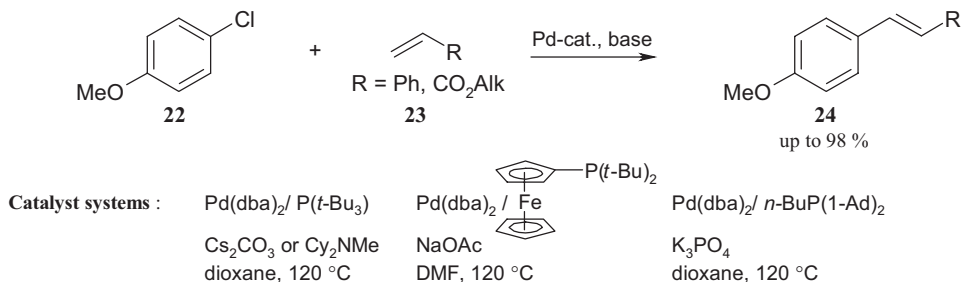


Scheme 10. Reverse enantioselectivity for the neutral and cationic pathways.

2.1.3.5 Heck Reactions of Aryl Chlorides

The profound industrial interest in extending the Heck reaction to the inexpensive but notoriously unreactive chlorohydrocarbons has triggered extensive studies in this field. Based on key pioneering work by Spencer [28], much progress has been achieved in recent years. The main challenge is to facilitate oxidative addition to stable C–Cl bonds (ca. 95 kcal mol^{−1}) while suppressing degradation reactions of the activating phosphine ligands.

Milstein et al. found that Pd complexes with chelating alkylphosphines such as bis(diisopropylphosphino)butane (dippb) efficiently catalyze the olefination of aryl chlorides with styrenes in the presence of elemental zinc [29]. Unfortunately, these electron-rich phosphines are apparently incompatible with electron-poor olefins such as acrylic acid derivatives. The latter were successfully coupled with activated chloroarenes by Herrmann et al., who used palladacycles or Pd-catalysts with heterocyclic carbenes [30].

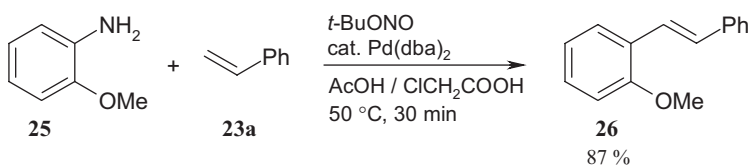


Scheme 11. Heck olefination of deactivated aryl chlorides.

Almost simultaneously, several groups developed efficient procedures for Heck reactions of deactivated chloroarenes **22** involving sterically crowded monodentate phosphines as activating ligand on the palladium (Scheme 11) [31]. Littke and Fu employed commercially available $P(t\text{-Bu})_3$, Hartwig $P(t\text{-Bu})_3$ or bis-*t*-butyl-ferrocenylphosphine, and Beller di(1-adamantyl)-*n*-butylphosphine. The use of biscyclohexylmethylamine as the base instead of alkali metal carbonates or phosphates significantly extends the scope of the Fu procedure in respect of the olefin partner.

2.1.3.6 Heck Reactions of Diazonium Salts

Another particularly attractive substrate class for industrial Heck reactions are the arenediazonium salts, because of their ready availability from anilines. Matsuda et al. found that for these highly reactive compounds, ligand-free $\text{Pd}(\text{dba})_2$ suffices as catalyst [32]. Even palladium catalysts on solid supports are highly effective [33]. The diazotization of an aniline **25** and its olefination can be performed separately, or in one pot (Scheme 12).



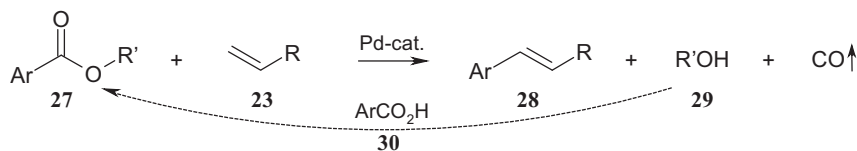
Scheme 12. Example for the one-pot diazotization – Heck reaction of an aniline.

2.1.3.7 Heck Reactions of Carboxylic Acid Derivatives

Blaser and Spencer discovered that when using aryl halides in the place of aryl halides, the olefination proceeds with decarbonylation, giving rise to the same vinyl arenes [34]. The ligandless catalysts are generated in situ from palladium halides – coordinating phosphines were found to hamper the decarbonylation step. Interestingly, Miura et al. reported that aryl chlorides can be olefinated efficiently, even in the absence of base, by using a rhodium catalyst; gaseous HCl is produced as byproduct [35].

For all standard Heck olefinations, stoichiometric amounts of base are required, leading to production of the corresponding quantities of waste salts. De Vries et al. first presented a possible solution to this long-standing problem by employing aromatic carboxylic anhydrides as the aryl source [36]. In the presence of a $\text{PdCl}_2/\text{NaBr}$ catalyst system carboxylic anhydrides were cleanly converted into one equivalent of the corresponding vinyl arene and one equivalent of the carboxylic acid, which in principle can be converted back into the starting anhydride.

Using optimized catalyst systems, even esters of electron-deficient phenols **27** or of enols were successfully coupled to olefins **23** to give the vinyl arenes **28**, along with CO and the corresponding phenol **29** or ketone, respectively



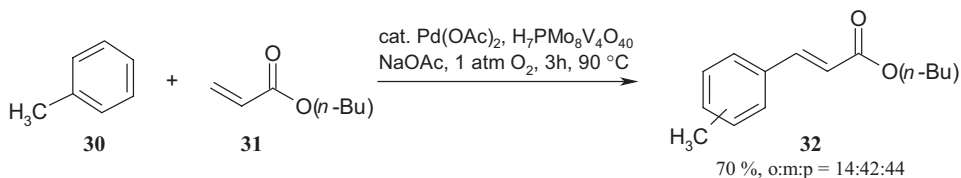
Scheme 13. Salt-free Heck olefination.

(Scheme 13) [37]. The phenols were successfully recycled into the starting material **27** by esterification with fresh carboxylic acid **30** (Scheme 4), thus demonstrating for the first time that the production of waste salts in Heck reactions is avoidable. This approach opens up interesting opportunities for the development of environmentally friendly Pd-catalyzed reactions.

2.1.3.8 Miscellaneous Substrates

In a process developed by Myers et al., aromatic carboxylic acids were directly employed as substrates for Heck olefinations, albeit in the presence of a large excess of silver carbonate [38]. This base both facilitates the decarboxylation step and acts as an oxidant, generating arylpalladium(II) intermediates. In related processes, arylphosphonic [39] and arylboronic acids [40] were used as aryl sources in the presence of an oxidant.

Under similar oxidative conditions, with activation of the aromatic C–H bond, some arenes could be used directly as aryl sources [41]. Unfortunately, by analogy with the Friedel–Crafts acylation, this reaction is regioselective for very few substrates only. High regioselectivity was, however, obtained if coordinating substituents on the arenes facilitate an orthopalladation reaction by a Pd(II) species [42]. After carbometallation and reductive elimination, Pd(0) is released, which has to be converted into the initial Pd(II) species in an extra oxidation step. Usually, quinines are used for this purpose, but in combination with certain heteropolyacids as cocatalysts even molecular oxygen can be employed as the oxidant.



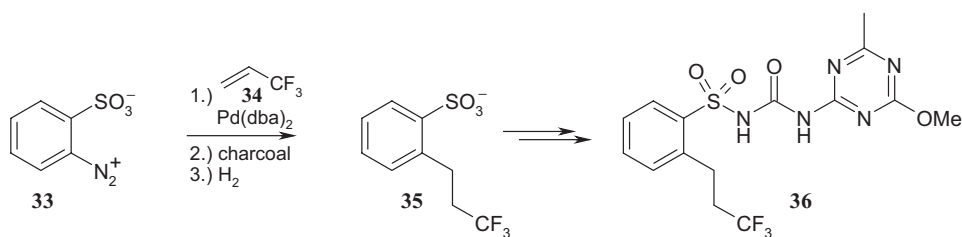
Scheme 14. Example for the oxidative Heck reaction of an arene.

As demonstrated in the preceding sections, the Heck reaction, although already a reliable and versatile tool, is still under development, and one can still expect major improvements in the coming years.

2.1.3.9 Industrial Applications

Several commercial products have been produced via Heck reactions on a scale in excess of one ton year⁻¹ [43]. The sunscreen agent 2-ethylhexyl-*p*-methoxycinnamate has been synthesized on a pilot scale by using Pd/C as the catalyst [44]. Albermarle produces Naproxen via a Heck reaction of 2-bromo-6-methoxynaphthalene with ethylene, followed by carbonylation of the product [45]. A key step in the production of Singulair (montelukast sodium), a leukotriene receptor antagonist for treatment of asthma, is Heck reaction of methyl 2-iodobenzoate with an allylic alcohol to give a ketone [43].

Heck olefination of a diazonium salt is a key step in the industrial synthesis of sodium 2-(3,3,3-trifluoropropyl)benzenesulfonate, en route to Novartis' sulfonyl-urea herbicide Prosulfuron (Scheme 15) [46]. Pd(dba)₂ (0.5–1.5 mol%, prepared in situ from PdCl₂), is used as catalyst. After completion of the arylation step, charcoal is added, thus directly providing a heterogeneous catalyst for the subsequent hydrogenation step and enabling easy removal of the now supported catalyst by filtration.



Scheme 15. Heck reaction in the synthesis of Prosulfuron.

The effective removal of residual palladium has become one of the most critical issues in the implementation of homogeneously catalyzed Heck reactions in industrial syntheses, particularly in the production of pharmaceuticals, in which tight specifications (sometimes less than 0.5 ppm Pd) must be met. Only very few scalable, inexpensive removal techniques are known [47], for example, binding of Pd to *N*-acetylcysteine and removal of the adduct by extraction or crystallization [48]. When such practical, inexpensive separation and recycling tools for palladium catalysts have been fully developed and industrially implemented, the Heck reaction will certainly find commercial use to the large extent that would be expected from its enormous synthetic utility.

Experimental

Heck Olefination of Aryl Bromides According to Spencer: Synthesis of Ethyl 4-Cyanocinnamate [18]

A mixture of palladium acetate (22.4 mg, 0.1 mmol) and tri(*o*-tolyl)phosphine (122 mg, 0.4 mmol) in DMF (20 mL) was stirred until a homogeneous solution had formed (5 min). A dry three-necked flask equipped with a magnetic stirrer, thermometer, and reflux condenser with argon bubbler and argon inlet-tube was

charged with DMF (49 mL), 4-bromobenzonitrile (9.10 g, 50.0 mmol), anhydrous sodium acetate (4.51 g, 55.0 mmol), and ethyl acrylate (5.96 g, 55.0 mmol). The reaction mixture was purged with argon and heated to 130 °C. Catalyst stock solution (1 mL) was added by means of a syringe and the reaction was stirred until complete conversion was indicated by gas chromatography (ca. 1 h), the reaction mixture was poured into water, extracted with dichloromethane, dried over MgSO_4 , filtered, and the volatiles were removed in vacuo. The residue was purified by distillation, giving the title compound in 97 % yield.

Heck Olefination of Aryl Chlorides According to Fu: Synthesis of (*E*)-3-(2-Methylphenyl)-2-methylacrylic Acid Methyl Ester [49]

An oven-dried Schlenk tube equipped with a magnetic stirrer bar was charged with $\text{Pd}_2(\text{dba})_3$ (12.9 mg, 0.014 mmol). The Schlenk tube was fitted with a rubber septum, evacuated and then refilled with argon. 2-Chlorotoluene (0.110 mL, 0.941 mmol), Cy_2NMe (0.220 mL, 1.03 mmol), $\text{P}(t\text{-Bu})_3$ (0.15 M stock solution in dioxane; 0.38 mL, 0.057 mmol), methyl methacrylate (0.110 mL, 1.03 mmol), and then dioxane (0.56 mL) were added by means of a syringe. The septum was replaced with a Teflon stopper and the reaction mixture was stirred at 110 °C for 24 h. The mixture was diluted with diethyl ether, filtered through a pad of silica gel with copious washing, concentrated, and purified by column chromatography (eluting with 5 % Et_2O –hexanes) to yield 158 mg (88 %) of the title compound as a clear, colorless liquid.

2.2

Wacker Oxidation

Lukas Hintermann

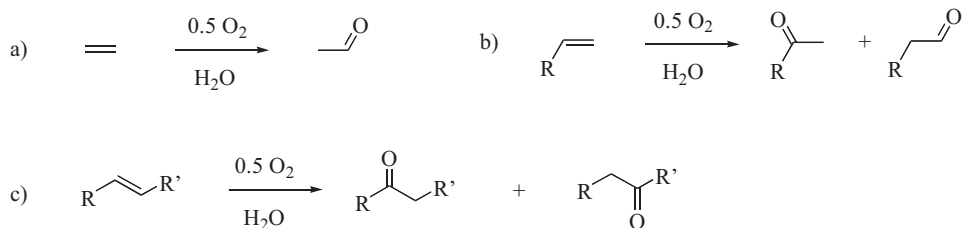
2.2.1

Introduction and Fundamental Examples

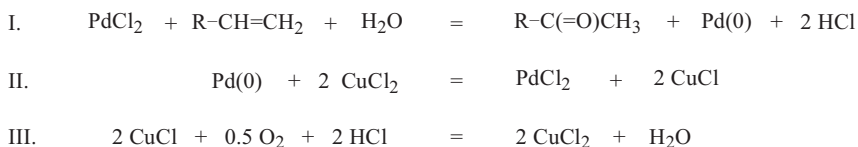
The palladium(II)-mediated oxidative coupling of olefins with oxygen-nucleophiles (ROH; water, alcohols, carboxylic acids) is a stoichiometric reaction with respect to Pd(II), resulting in an oxygenated product and Pd(0). To convert Pd(0) back to Pd(II) and start a new reaction cycle, a *reoxidation reaction* (which can itself be stoichiometric or catalytic) using a *terminal oxidant* is required. In this way, the overall process becomes catalytic with respect to the expensive Pd salt.

The first and foremost reaction of this type is the now classical Wacker–Hoechst oxidation [1–4] of ethene to ethanal (acetaldehyde) by means of a $\text{PdCl}_2/\text{CuCl}_2$ as catalyst and O_2 as terminal oxidant (Scheme 1, a).

This process with its ingenious Cu(I)/Cu(II)/ O_2 reoxidation cycle for Pd(0) (Scheme 2) was highly influential in the further development of homogeneous catalysis, because it demonstrated that even an “exotic” and expensive metal such as palladium can be used in the large-scale production of cheap base-chemicals.



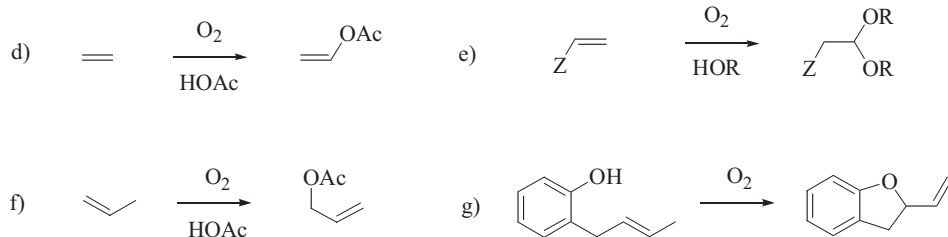
Scheme 1. Palladium-mediated oxidative coupling reactions of olefins and water.



Scheme 2. The Cu(I)/Cu(II)-reoxidation system in the Wacker–Hoechst olefin oxidation reaction.

Application of Wacker chemistry to higher olefins can give isomeric products (Scheme 1, b and c), but with terminal olefins, methyl ketones are usually formed (Scheme 1, b). On an industrial scale, propene is converted to acetone [4]. Additional examples of higher olefin oxidation were reported by the Wacker group [1], but the reaction did not find much use in synthetic chemistry before it was adapted for use with organic solvents, and reliable reoxidation systems working in such media were found. In that respect, Moiseev et al. observed that benzoquinone (BQ) is a rapid and homogeneous stoichiometric reoxidant for Pd(0) [5], and practical procedures for synthetic oxidations were presented by Clement and Selwitz in 1964 [6], who also introduced aqueous *N,N*-dimethylformamide (DMF) as a solvent of choice. Later, influential work came from Tsuji and coworkers, who popularized CuCl/O₂ in place of CuCl₂/O₂ as a powerful and reliable reoxidation system [7–10] which, apparently, produces none of the chlorinated side-products of the Wacker process and operates under almost neutral conditions. Although water is the oxygen-nucleophile in the original Wacker reaction, mechanistically similar oxidative couplings with carboxylic acids give rise to vinyl esters (Scheme 3, d) and alcohols give acetals [11–13] (Scheme 3, e). In fact, the palladium-catalyzed coupling of acetic acid with ethene and O₂ as direct terminal oxidant (Cu is not necessary) to produce vinyl acetate is now also an important industrial process, based on the discovery by Moiseev et al. in 1960 [14].

Examples of oxidative coupling to vinyl derivatives remain limited in number, however, because the reaction takes a different course whenever allylic hydrogen atoms are present in a substrate (Scheme 3, f and g). Under these conditions allylic sp³ C–H bonds are activated and such reactions are therefore *allylic oxidations* (Section IV.1.2.4). In recent years, however, several examples of reactions of type g (Scheme 3) have been performed enantioselectively and called *asymmetric*



Scheme 3. Palladium-mediated coupling reactions between olefins and alcohols or carboxylic acids.

Wacker reactions, which is why we refer to them here [12, 15–17]. Finally, the general concept of a Wacker reaction could be regarded as the palladium-catalyzed oxidative coupling of heteronucleophiles and olefins, and this can obviously be extended to nitrogen nucleophiles and others [18]; conversely, the principle of the Cu(I)/Cu(II)/O₂ reoxidation system for Pd(0) can be applied to other oxidation reactions (for example that of CO to CO₂), but the present overview is limited to sp²-C–H activation in olefins.

2.2.2

Mechanism

The overall mechanistic pathway of the Wacker reaction is easily rationalized, but details of the individual reaction steps are still a matter of discussion and continuing research [19–21]. Considering the manifold reaction conditions and reoxidation systems known from the literature, *a single mechanism is certainly not operating in all cases*. A good starting point is the classical Wacker–Hoechst ethanal synthesis [4], a simplified catalytic cycle of which is depicted in Fig. 1 [19–21]. Starting from tetrachloropalladate(II) (**A**), ligand exchange with ethene leads to a π -complex **B**, in which the olefin is activated toward nucleophilic attack by water (vide infra), resulting in a 2-hydroxyethylpalladium species **C**. Now, β -hydrogen elimination leads to a hydridopalladium species **D**, and reinsertion results in a 1-hydroxyethylpalladium species **E**. There is neither dissociation of vinyl alcohol nor exchange of protons from **D**, as shown by isotope-labeling studies, because ethene in D₂O yields ethanal free from deuterium [2].

Subsequently, **E** releases ethanal to give a Pd(0) species which is reoxidized to Pd(II) by means of Cu(II), possibly via dinuclear species such as **F**, and Cu(II) is regenerated from Cu(I) by reaction with O₂ and HCl. From the kinetics of the Wacker oxidation, which are roughly expressed [4, 22] by the equation:

$$-d[\text{C}_2\text{H}_4]/dt = k [\text{C}_2\text{H}_4][\text{PdCl}_4^{2-}]/[\text{H}^+][\text{Cl}^-]^2$$

it can be concluded that **B** undergoes at least one additional ligand exchange of Cl[−] by H₂O and loss of a proton, occurring *before* the rate-determining step. What exactly happens on a molecular level is not yet clear, but the interpretation is

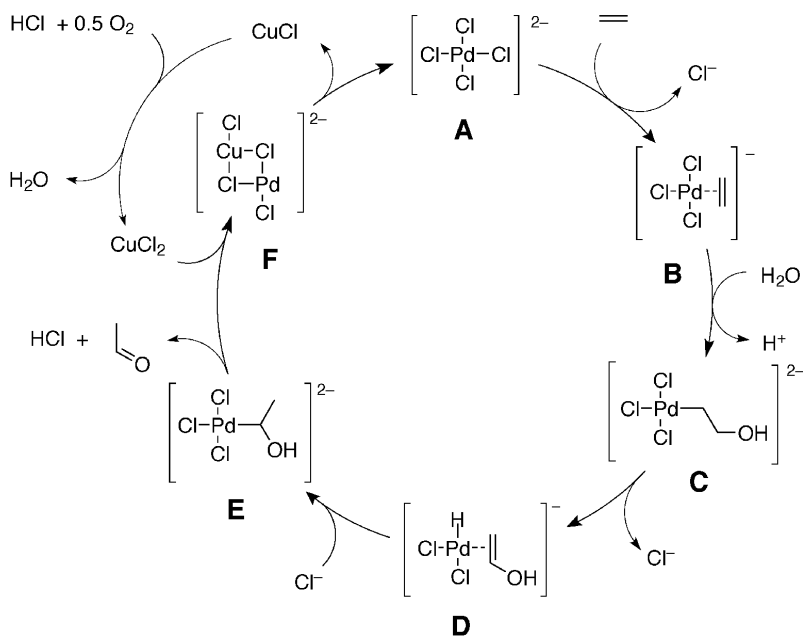
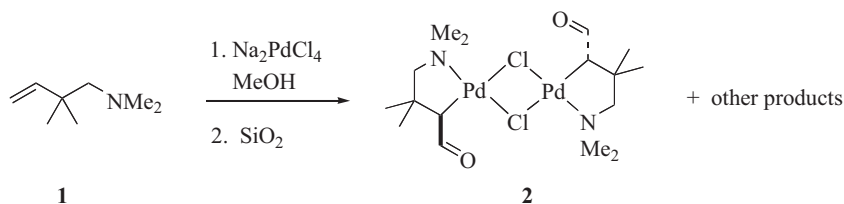


Figure 1. Schematic catalytic cycle of the Wacker–Hoechst ethene oxidation.

directly connected to the debate about the stereochemistry of *hydroxypalladation*, which might be anti, because of external attack of water on coordinated ethene [20, 21], or alternatively syn, with insertion of ethene into a Pd–OH bond [4, 19]. Anti hydroxypalladation has been established in many model reactions with palladium–olefin complexes and even for ethene at high chloride concentrations [20], but syn hydroxypalladation is not excluded for ethene at low chloride concentrations [23]. In fact, a recent investigation of the cyclization of ortho allylphenols nicely illustrates that the stereochemistry of oxypalladation can depend on the presence of chloro ligands on palladium(II) [24]. For higher olefins the mechanism is probably similar, but it is an additional challenge to explain and predict the *regioselectivity* of the Wacker reaction on mechanistic grounds. Deviations from the usual Markovnikov regioselectivity (methyl ketones from terminal olefins) are not uncommon and are usually explained by invoking directing effects of coordinating functional groups within the substrate [8, 25, 26]. In such cases, regioselective hydroxypalladation of the olefin is governed by reaction pathways via kinetically favored cyclopalladated intermediates. An illustration for this comes from an X-ray structure of a dimeric five-membered cyclopalladated complex **2** (Scheme 4) which is formed via oxypalladation from olefin **1** [27]:

Intramolecular coordination is apparently responsible for most examples of regioselective Wacker oxidations of *internal* olefins, but *electronic* effects are also operating [28], specifically in acceptor-substituted olefins. Steric effects are currently not well explored [8]. Recent theoretical studies on the mechanism of the Wacker and related reactions are available elsewhere [29, 30].



Scheme 4. Palladacycle from the Pd-mediated oxidation of a homoallylic tertiary amine.

2.2.3

Scope and Limitations


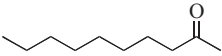
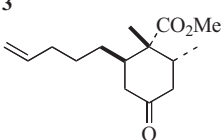
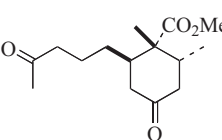


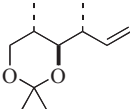
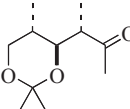
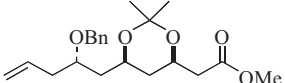
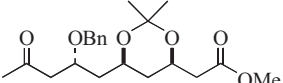


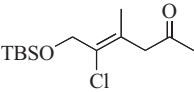
The major emphasis in this section is on examples from the recent literature, thus the priority of the cited authors for a certain type of reaction cannot generally be assumed. Many earlier examples will be found in the reviews by Tsuji [8, 10].

2.2.3.1 Reactions Initiated by the Addition of Water to Terminal Alkenes

Terminal non-functionalized alkenes react selectively to give methyl ketones (Table 1), with the corresponding aldehydes as by-products in variable amounts. In terms of synthetic planning, the terminal alkene can be regarded as a masked methyl ketone. The reaction has been performed on a wide range of substrates from simple olefins, for example 1-decene (**3**, gives 2-decanone **4**) [9] to fairly complex intermediates bearing many functional groups (**5** to **6** [31], **9** to **10** [32], **11** to **12** [33]) or even polymers bearing vinyl groups (**7** to **8**) [34]. The “vinyl to acetyl” conversion has been included in various *synthetic sequences*, in which the generation of particular olefins is followed by a Wacker oxidation and then another specific reaction involving the methyl ketone. Examples [8, 10] include: (1) cyclopentenones are generated by α -allylation of ketones via subsequent oxidation and aldol-condensation. (2) Analogously, annelation of cyclohexenones is possible via oxidation of α -3-butenyl ketones, then aldol-condensation. (3) If asymmetric allylation of an aldehyde to a homoallylic alcohol is followed by O-protection and Wacker oxidation, the equivalent of an asymmetric acetone aldol reaction is achieved (for the second part, cf. **11** to **12** [33]), etc. An elegant new one-pot tandem sequence combines the palladium-catalyzed chloroallylation of alkynes (e.g. **13** with **14**) and subsequent Wacker oxidation (simply by adding CuCl and O₂) of the intermediary chlorodiene **15** (not drawn) [35].

Among the most popular reaction conditions for this conversion are those popularized by Tsuji and coworkers (experiment 1, below), using 10 mol% PdCl₂ and 1 equiv. CuCl in aqueous DMF under an atmosphere of O₂ at room temperature [9]. Everything can be varied, however. In terms of solvents, alcohols tend to give faster reactions, but are said to speed up olefin isomerization. CuCl₂·2H₂O can be used as a reoxidant, but chlorinated side-products are potentially formed. This is precluded in halide-free systems, e.g. with Pd(OAc)₂ and Cu(OAc)₂/O₂,

Table 1. Wacker oxidation of terminal olefins.

Starting materials	Products	Yield (%)	Ref.
 3	 4	65–73	9
 5	 6	65	31
 7	 8	n. d.	34
 9	 10	84 ^a	32
 11	 12	73	33
  13 + 14	 16	66	35

Reaction conditions similar to those in experiment 1, below, plus

(a) Pd(OAc)₂, Cu(OAc)₂/O₂ reoxidant

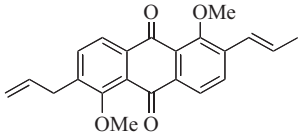
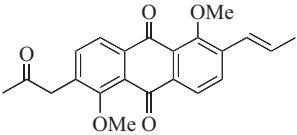


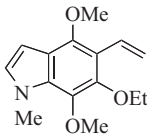
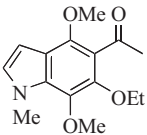
which are also recommended for acid-sensitive substrates such as **9** [32]. Benzoquinone (BQ) is a very interesting reoxidant for synthetic purposes, resulting in rapid reactions in homogeneous solution and enabling rather low catalyst loadings (e.g. ≤1 mol%; experiment 3, below) [5, 6]. A particularly active system for olefin oxidation is obtained with Pd(OAc)₂ and BQ, if HClO₄ (0.3 M) is present in the reaction medium [36] (experiment 2). In addition, many variations of reaction me-

dium and reoxidation system have been suggested but, currently, none is widely applied in synthesis. In an interesting line of research, reaction conditions have been developed in which O_2 is used as a *direct* terminal oxidant for Pd(0) [37].

2.2.3.1.1 Specific Substrates

Although allyl-arenes are prone to olefin isomerization, several successful reactions have been performed, for example in the chemoselective oxygenation of **22** to aryl-acetone **23** (Table 2) [38]. Allyl alcohols sometimes react sluggishly, but examples with high ketone selectivity are known, for example the oxidation of tertiary alcohol **24** to α -hydroxyketone **25** [39].

Table 2. Oxidation of specific terminal olefins.

Starting materials	Products	Yield (%)	Ref.
 22	 23	75	38
 24	 25	88 ^a	39
 26	 27	77	40

Reaction conditions similar to those in experiment 1, below, plus

(a) BQ as terminal oxidant.

2.2.3.1.2 Styrenes

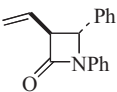
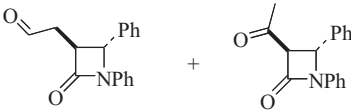
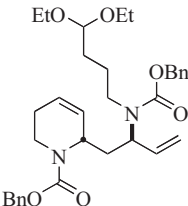
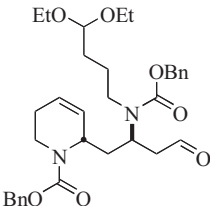
The oxidation of styrenes under Wacker conditions is relatively slow and not always regioselective, but useful yields of acetophenones have been obtained, for example the highly substituted **27** from olefin **26** [40]. Acetophenones, on the other hand, have consistently been obtained in yields higher than 75 % by using a Pd-diketonate complex with *t*-BuOOH as oxidant in a biphasic $C_8F_{17}Br/C_6H_6$ me-

dium [41]. The oxidation with Pd(II)/*t*-BuOOH is mechanistically distinct from the usual Wacker oxidation, and is rather general for terminal olefins [42].

2.2.3.1.3 Inversion of Regioselectivity in Terminal Alkene Oxidation

The basic *Markovnikov* selectivity pattern is partially or fully overrun in the presence of neighboring coordinating groups within the olefin substrate (Section 2.2.2). Known functionalities where inversed selectivity can occur include 3-alkenoylamides (e.g. **17** reacts to give a mixture of **18** and **19**, Table 3) [43], homoallyl esters and alcohols, allyl ethers (but not necessarily allyl alcohols) [44], allyl amines, allyl amides, or carbamates (cf. **20** to **21**) [45], allyl sulfides [46] or 1,5-dienes [47]. As a matter of fact, aldehyde by-products are quite normal in Wacker reactions, but tend to be overlooked.

Table 3. Inversion of regioselectivity in terminal alkene oxidation.

Starting materials	Products	Yield (%)	Ref.
 17	 18 19	65 (18) 5 (19)	43
 20	 21	76	45

Reaction conditions similar to those in experiment 1

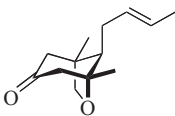
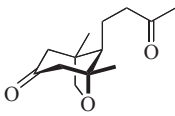
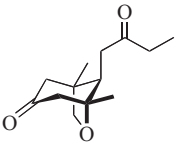
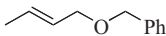
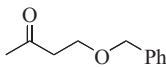
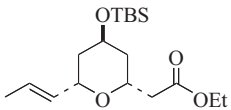
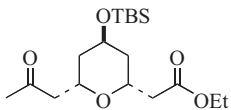
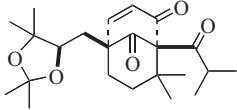
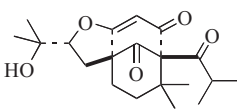
A catalyst system based on the complex PdCl(NO₂)(MeCN)₂ with CuCl₂/O₂ as reoxidant in *t*-BuOH as solvent has a tendency to give high selectivity for aldehydes [48], but preparative applications remain to be explored.

2.2.3.2 Reactions Initiated by Addition of Water to Internal Alkenes

Internal olefins react more slowly than terminal olefins, and mixtures of regioisomers are usually formed. Accompanying olefin isomerization can further complicate product selectivity. Despite these words of warning, the reaction can still give satisfactory results (Table 4), for example in the final step of the total synthesis of annuonone A (**29**), which involves oxidation of bicyclic olefin **28** [49]. A

small amount of regioisomer **30** is formed, though. The key to high regioselectivity is the presence of certain coordinating or electronically directing groups within the substrate: Allyl ethers and esters yield β -alkoxyketones (**31** to **32**) and β -acyloxyketones, respectively, with rather high selectivity [10, 50]. The α -propenyl-tetrahydropyran **33** was converted to the building block **34** for total synthesis of leucascandrolide A [51]. Homoallyl esters are regioselectively converted into the 4-acyloxyketones [10].

Table 4. Oxidation of internal olefins.

Starting materials	Products	Yield (%)	Ref.
 28	 29	 30	54 (29) 16 (30) 49
 31	 32	67	10
 33	 34	86	51
 35	 36	69 ^a	54

Reaction conditions are similar to those in experiment 1, plus (a)
 Na_2PdCl_4 (40 mol%)/*t*-BuOOH in HOAc/ H_2O

1-Propenylarenes (β -methylstyrenes) are oxidized with varying degrees of regioselectivity, depending on the electronic effects of the substituents in the aromatic ring [28, 52]. Reactions using Na_2PdCl_4 as catalyst in aqueous acetic acid with either H_2O_2 or *t*-BuOOH as oxidant convert 2-alkenones and 2-alkenoates to

β -diketones or β -ketoesters, respectively [8, 10, 53], e.g. alkenone **35** was transformed to a tricyclic ether **36** by oxidation, followed by acidic cleavage of the acetal unit and condensation [54]. 3-Alkenones and 3-alkenoates are oxidized to 1,4-difunctionalized compounds while 4-Alkenones give 1,5-dicarbonyl compounds [8, 10]. The regioselectivity of oxidation can be difficult to predict in substrates containing multiple functional groups [44]. Changes of protecting groups can also affect the reaction selectivity [44].

2.2.3.3 Reactions Initiated by the Addition of Alcohols or Carboxylic Acids to Alkenes

If carboxylic acids and alcohols act as nucleophiles in the Wacker reaction, the products are vinyl esters or acetals, respectively. As mentioned, the substrate scope of these oxidations is usually limited to olefins not bearing hydrogen in allylic position, because of competing *allylic oxidation*.

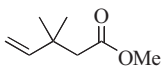
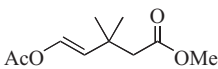
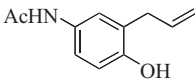
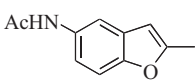

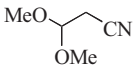
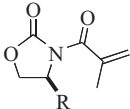
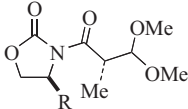

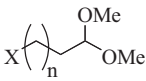
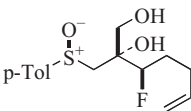
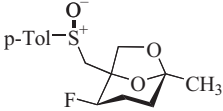
2.2.3.3.1 ROH Addition then Elimination to Vinyl Derivatives

The industrial synthesis of vinyl acetate [14] via palladium-catalyzed oxidative coupling of acetic acid and ethene using direct O₂ reoxidation has already been mentioned (Scheme 3, *d*). Some NaOAc is required in the reaction medium, and catalysis by Pd clusters, as alternative to Pd(II) salts, was proposed to proceed with altered reaction characteristics [14]. Similarly, the alkenyl ester **37** (Table 5) containing an “isolated” vinyl group yields the expected enol acetate **38** [55] whereas allylphenol **39** cyclizes to benzofuran **40** with double bond isomerization [56].

2.2.3.3.2 Acetalization Reactions

Acetals result from oxidative coupling of alcohols with electron-poor terminal olefins followed by a second, redox-neutral addition of alcohol [11–13]. Acrylonitrile (**41**) is converted to 3,3-dimethoxypropionitrile (**42**), an intermediate in the industrial synthesis of thiamin (vitamin B1), by use of an alkyl nitrite oxidant [57]. A stereoselective acetalization was performed with methacrylates **43** to yield **44** with variable *de* [58]. Rare examples of *intermolecular* acetalization with nonactivated olefins are observed with chelating allyl and homoallyl amines and thioethers (**45**, give acetals **46**) [46]. As opposed to intermolecular acetalizations, the *intramolecular* variety do not require activated olefins, but a suitable spatial relationship of hydroxy groups and the alkene [13]. Thus, Wacker oxidation of enediol **47** gave bicyclic acetal **48** as a precursor of a fluorinated analogue of the pheromone frontalin [59].

Table 5. Carboxylic acids and alcohols as nucleophiles in the Wacker oxidation of sp^2 -C–H bonds.

Starting materials	Products	Yield (%)	Ref.
 37	 38	63 ^a	55
 39	 40	92 ^b	56
 41	 42	n.a. ^c	57
 43	 44	up to 92% ^d de up to 95%	58
 45	 46	up to 85% ^e	46
 47	 48	80% ^f	59

Reaction conditions: (a) HOAc, O₂ (5 MPa), Pd(OAc)₂ (2 mol%), 80 °C, 22 h. (b) Cu(OAc)₂·H₂O, LiCl, PdCl₂ (2 mol%), DMF/H₂O, r.t. (c) PdCl₂, MeOH, MeONO, N₂O, O₂. (d) PdCl₂ (10 mol%), CuCl (100 mol%), DME/MeOH, r.t. (e) CuCl₂ (300 mol%), Li₂PdCl₄ (10 mol%), MeOH, 50 °C. (f) PdCl₂ (59 mol%), CuCl₂, DME, r.t.

Experimental

Olefin Oxidation Using a CuCl/O₂ Reoxidation System (Tsuji Conditions), General Working Procedure. Adapted From Ref. [9]

A mixture of PdCl₂ (10 mol%) and CuCl (100 mol%) in *N,N*-dimethylformamide/H₂O (7:1) is stirred vigorously for 1 h under an atmosphere of oxygen. The olefin is added and the reaction mixture stirred at r.t. until consumption of the starting material. The reaction is quenched with dilute HCl and extracted with ether. The ratio of reagents and solvents can be varied widely as described in many examples throughout this chapter. The oxygen atmosphere is maintained by use of a simple balloon technique. Reactions will also proceed in air, but at a slower rate.

Fast Olefin Oxidation Using Pd(OAc)₂ and Benzoquinone in Acetonitrile/H₂O/HClO₄, General Working Procedure. Adapted From Refs [25, 36]

A mixture of 0.2 mmol Pd(OAc)₂ (2 mol%), 10 mmol benzoquinone, and 1 mL perchloric acid (72 %) in 50 mL acetonitrile–H₂O (7:1) is stirred under Ar at r.t. until complete dissolution. The olefin (10 mmol) is added and the reaction mixture stirred at r.t. (aliphatic olefins, cyclohexene) or 60 °C (styrene, cycloheptene, internal olefins) until completion of the reaction (from 10 min to 90 min), as judged by TLC. The mixture is poured into diethyl ether and washed with aqueous NaOH (30 %). The aqueous layer is extracted with ether. The combined organic layers are dried over MgSO₄, filtered, and the solvent is evaporated. The crude product is purified by chromatography.

Oxidation of 1-Octene, Using PdCl₂/Benzoquinone, at Low Catalyst Loading. Conditions Adapted From Ref. [6]

A solution of 1-octene (5.00 g, 44.55 mmol) in MeOH (5 mL) was slowly added to a solution of PdCl₂(MeCN)₂ (52 mg, 0.2 mmol, 0.45 mol%), and benzoquinone (5.40 g, 50 mmol) in 25 mL MeOH and 3 mL H₂O, held at 60 °C. After 5 h at 60 °C, the reaction mixture was cooled to r.t. and the solvent removed by rotary evaporation. The residue was dissolved in *t*-BuOMe and the organic solution washed with 2 M HCl (2×), 2 M NaOH (3×, removes hydroquinone) and water (1×). After drying (Na₂SO₄) and evaporation, the residual oil was distilled in vacuo (75 °C/ca. 80 mbar) to give 4.01 g (70 %) of a fruity smelling clear liquid, consisting of octanones. GC–MS: Peak area (2-octanone:3-octanone:4-octanone:octanal) = 82:11:7:<0.5; substances were identified from their mass spectra; no olefins detected. ¹H NMR (CDCl₃): 2-octanone (82 %): δ = 0.88 (t, *J* = 7.1 Hz, 3 H, H-C(8)), 1.20–1.08 (m, 6 H, H-C(7,6,5)), 1.63–1.51 (m, 2 H, H-C(4)), 2.13 (s, 3 H, H-C(1)), 2.42 (t, *J* = 7.4 Hz, 2 H, H-C(3)). 3-octanone, selected signal (12 %): 1.05 (t, *J* = 7.3 Hz, 3 H, H-C(1)); 4-octanone; overlapping signals only; octanal, selected signal (<1 %): 9.77 (t, *J* = 1.9 Hz, 1 H, H-C(1)).

References to Chapter 2 – C–H Transformation at Alkenes

References to Section 2.1

- 1 R. F. Heck, *J. Am. Chem. Soc.* **1968**, *90*, 5518–5546 (7 papers).
- 2 T. Mizoroki, K. Mori, A. Ozaki, *Bull. Chem. Soc. Japan* **1971**, *44*, 581.
- 3 R. F. Heck, J. P. Nolley, Jr., *J. Org. Chem.* **1972**, *37*, 2320–2322.
- 4 P. Fitton, J. E. McKeon, *J. Chem. Soc., Chem. Commun.* **1968**, 4–6; P. Fitton, M. P. Johnson, J. E. McKeon, *ibid.*, 6–7.
- 5 H. A. Dieck, R. F. Heck, *J. Am. Chem. Soc.* **1974**, *96*, 1133–1136.
- 6 A. de Meijere, F. E. Meyer, *Angew. Chem. Int. Ed.* **1994**, *33*, 2379–2411; I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009–3066.
- 7 Domino reactions: A. de Meijere, S. Bräse, *J. Organomet. Chem.* **1999**, *576*, 88–110.
- 8 Enantioselective Heck reactions: M. Shibasaki, E. M. Vogl, *J. Organomet. Chem.* **1999**, *576*, 1–15; O. Loiseleur, M. Hayashi, M. Keenan, N. Schmees, A. Pfaltz, *ibid.*, 16–22.
- 9 G. T. Crisp, *Chem. Soc. Rev.* **1998**, *27*, 427–436.
- 10 H. M. Senn, T. Ziegler, *Organometallics* **2004**, *23*, 2980–2988.
- 11 K. Albert, P. Gisdakis, N. Roesch, *Organometallics* **1998**, *17*, 1608–1616.
- 12 K. Fagnou, M. Lautens, *Angew. Chem. Int. Ed.* **2002**, *41*, 26–47.
- 13 C. Amatore, A. Jutand, *Acc. Chem. Res.* **2000**, *33*, 314–321.
- 14 S. Kozuch, S. Shaik, A. Jutand, C. Amatore, *Chem. Eur. J.* **2004**, *10*, 3072–3080.
- 15 L. J. Gooßen, D. Koley, H. Hermann, W. Thiel, *Chem. Comm.* **2004**, 2141–2143.
- 16 H. von Schenck, B. Kermack, M. Svensson, *J. Am. Chem. Soc.* **2003**, *125*, 3503–3508.
- 17 R. Grigg, V. Sridharan, P. Stevenson, T. Worakun, *J. Chem. Soc., Chem. Commun.* **1986**, 1697–1699.
- 18 A. Spencer, *J. Organomet. Chem.* **1983**, *258*, 101–108.
- 19 T. Jeffery, *Chem. Comm.* **1984**, 1287–1289; T. Jeffery, *Tetrahedron Lett.* **1985**, *26*, 2667–2670.
- 20 T. Jeffery, *Tetrahedron* **1996**, *52*, 10113–10130.
- 21 M. T. Reetz, J. G. de Vries, *Chem. Comm.* **2004**, 1559–1563.
- 22 A. H. M. de Vries, J. M. C. A. Mulders, J. H. M. Mommers, H. J. W. Henderickx, J. G. de Vries, *Org. Lett.* **2003**, *5*, 3285–3288.
- 23 L. F. Tietze, K. Heitmann, T. Raschke, *Synlett* **1997**, 35–37.
- 24 Y. Zhang, G. Z. Wu, G. Agnel, E. Negishi, *J. Am. Chem. Soc.* **1990**, *112*, 8590–8592.
- 25 Y. Sato, M. Sodeoka, M. Shibasaki, *J. Org. Chem.* **1989**, *54*, 4738–4739.
- 26 O. Loiseleur, P. Meier, A. Pfaltz, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 200–202.
- 27 A. Ashimori, B. Bachand, L. E. Overman, D. J. Poon, *J. Am. Chem. Soc.* **1998**, *120*, 6477–6487.
- 28 A. Spencer, *J. Organomet. Chem.* **1984**, *270*, 115–120.
- 29 M. Portnoy, Y. Ben-David, D. Milstein, *Organometallics* **1993**, *12*, 4734–4735.
- 30 W. A. Herrmann, M. Elison, J. Fischer, C. Köcher, G. R. J. Artus, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2371–2373; W. A. Herrmann, V. P. W. Böhm, C.-P. Reisinger, *J. Organomet. Chem.* **1999**, *576*, 23–41.
- 31 A. F. Littke, G. C. Fu, *Angew. Chem. Int. Ed.* **2002**, *41*, 4176–4211.
- 32 K. Kikukawa, K. Maemura, Y. Kiseki, F. Wada, T. Matsuda, *J. Org. Chem.* **1981**, *46*, 4885–4888.
- 33 M. Beller and K. Kühlein, *Synlett*, **1995**, 441–442.
- 34 H.-U. Blaser, A. Spencer, *J. Organomet. Chem.* **1982**, *233*, 267–274.
- 35 T. Sugihara, T. Satoh, M. Miura, M. Nomura, *Angew. Chem. Int. Ed.* **2003**, *42*, 4672–4674.
- 36 M. S. Stephan, A. J. J. M. Teunissen, G. K. M. Verzijl, J. G. De Vries, *Angew. Chem. Int. Ed.* **1998**, *37*, 662–664.
- 37 L. J. Gooßen, J. Paetzold, *Angew. Chem. Int. Ed.* **2002**, *41*, 1237–1241;

- L. J. Gooßen, J. Paetzold, *Angew. Chem. Int. Ed.* **2004**, 43, 1095–1098.
- 38 A. G. Myers, D. Tanaka, M. R. Mannion, *J. Am. Chem. Soc.* **2002**, 124, 11250–11251.
- 39 A. Inoue, H. Shinokubo, K. Oshima, *J. Am. Chem. Soc.* **2003**, 125, 1484–1485.
- 40 M. M. S. Andappan, P. Nilsson, H. von Schenck, M. Larhed, *J. Org. Chem.* **2004**, 69, 5212–5218.
- 41 M. Tani, S. Sakaguchi, Y. Ishii, *J. Org. Chem.* **2004**, 69, 1221–1226.
- 42 M. D. K. Boele, G. P. F. van Strijdonck, A. H. M. de Vries, P. C. J. Kamer, J. G. de Vries, P. W. N. M. van Leeuwen, *J. Am. Chem. Soc.* **2002**, 124, 1586–1587.
- 43 J. G. de Vries, *Can. J. Chem.* **2001**, 79, 1086–1092.
- 44 D. C. Caskey, WO 9010617 (1990).
- 45 http://www.albemarle.com/core_check_right.htm; T.-C. Wu, US 5536870 (1996).
- 46 P. Baumeister, G. Seifert, H. Steiner, EP 584043 A1 (1994).
- 47 C. E. Garrett, K. Prasad, *Adv. Synth. Catal.* **2004**, 346, 889–900.
- 48 M. Villa, V. Cannata, A. Rosi, P. Allegrini, WO 9851646 (1998).
- 49 A. F. Littke, G. C. Fu, *J. Am. Chem. Soc.* **2001**, 123, 6989–7000.
- 7 J. Tsuji, I. Shimizu, K. Yamamoto, *Tetrahedron Lett.* **1976**, 34, 2975–2976.
- 8 J. Tsuji, *Synthesis* **1984**, 369–384.
- 9 J. Tsuji, H. Nagashima, H. Nemoto, *Organic Syntheses* **1984**, 62, 9–13, and *Coll. Vol. VII*, 137–139.
- 10 J. Tsuji in *Comprehensive Organic Synthesis*, B. M. Trost, I. Fleming (Eds.), Vol. 7, pages 449–468, Pergamon Press **1991**.
- 11 W. G. Lloyd, B. J. Luberoff, *J. Org. Chem.* **1969**, 34, 3949–3952.
- 12 T. Hosokawa, S.-I. Murahashi, *Acc. Chem. Res.* **1990**, 23, 49–54.
- 13 T. Hosokawa, S.-I. Murahashi in *Handbook of Organopalladium Chemistry for Organic Synthesis*, E.-I. Negishi (Ed.), pages 2141–2192, John Wiley & Sons **2002**.
- 14 I. I. Moiseev, M. N. Vargaftik in *Applied Homogeneous Catalysis with Organometallic Compounds*, B. Cornils, W. A. Herrmann (Eds.), 2nd ed., Vol. 1, pages 406–412, Wiley-VCH **2002**.
- 15 Y. Uozumi, K. Kato, T. Hayashi, *J. Am. Chem. Soc.* **1997**, 119, 5063–5064.
- 16 M. A. Arai, M. Kuraishi, T. Arai, H. Sasai, *J. Am. Chem. Soc.* **2001**, 123, 2907–2908.
- 17 R. M. Trend, Y. K. Ramtohl, E. M. Ferreira, B. M. Stoltz, *Angew. Chem. Int. Ed.* **2003**, 42, 2892–2895.
- 18 J. M. Takacs, S. Vayalakkada in: *Science of Synthesis, Organometallics*, Vol. 1., pages 319–387, Georg Thieme **2001**.
- 19 P. M. Henry in *Handbook of Organopalladium Chemistry for Organic Synthesis*, E.-I. Negishi (Ed.), pages 2119–2139, John Wiley & Sons **2002**.
- 20 J. E. Bäckvall, B. Åkermark, S. O. Ljunggren, *J. Am. Chem. Soc.* **1979**, 101, 2411–2416.
- 21 J. K. Stille, R. Divakaruni, *J. Organomet. Chem.* **1979**, 169, 239–248.
- 22 I. I. Moiseev, O. G. Levanda, M. N. Vargaftik, *J. Am. Chem. Soc.* **1974**, 96, 1003–1007.
- 23 O. Hamed, P. M. Henry, C. Thompson, *J. Org. Chem.* **1999**, 64, 7745–7750.
- 24 T. Hayashi, K. Yamasaki, M. Mimura, Y. Uozumi, *J. Am. Chem. Soc.* **2004**, 126, 3036–3037.
- 25 H. Pellissier, P.-Y. Michellys, M. Santelli, *Tetrahedron* **1997**, 53, 7577–7586.

References and Notes to Section 2.2

- 1 J. Smidt, W. Hafner, R. Jira, J. Sedlmeier, R. Sieber, R. Rüttinger, H. Kojer, *Angew. Chem.* **1959**, 71, 176–182.
- 2 J. Smidt, W. Hafner, R. Jira, R. Sieber, J. Sedlmeier, A. Sabel, *Angew. Chem.* **1962**, 74, 93–102.
- 3 J. Smidt, W. Hafner, R. Jira, R. Rüttinger, to Consortium für elektrochemische Industrie, DP 1049845, **1959**.
- 4 R. Jira in: *Applied Homogeneous Catalysis with Organometallic Compounds*, B. Cornils, W. A. Herrmann (Eds.), 2nd ed., Vol. 1, pages 386–405, Wiley-VCH **2002**.
- 5 I. I. Moiseev, M. N. Vargaftik, Y. K. Syrkin, *Dokl. Akad. Nauk SSSR* **1960**, 133, 377–380. *Chem. Abstr.* **1960**, 54, 24350g.
- 6 W. H. Clement, C. M. Selwitz, *J. Org. Chem.* **1964**, 29, 241–243.

- 26 H. Pellissier, P.-Y. Michellys, M. Santelli, *Tetrahedron* **1997**, 53, 10733–10742.
- 27 E. C. Alyea, S. A. Dias, G. Ferguson, A. J. McAlees, R. McCrindle, P. J. Roberts, *J. Am. Chem. Soc.* **1977**, 99, 4985–4989.
- 28 M. J. Gaunt, J. Yu, J. B. Spencer, *Chem. Commun.* **2001**, 1844–1845.
- 29 P. E. M. Siegbahn, *J. Phys. Chem.* **1996**, 100, 14672–14680.
- 30 D. D. Kragten, R. A. van Santen, J. J. Lerou, *J. Phys. Chem. A* **1999**, 103, 80–88.
- 31 R. Paczkowski, C. Maichle-Mössmer, M. E. Maier, *Org. Lett.* **2000**, 2, 3967–3969.
- 32 A. B. Smith, Y. S. Cho, G. K. Friestad, *Tetrahedron Lett.* **1998**, 39, 8765–8768.
- 33 C. Schneider, F. Tolsdorf, M. Rehfeuter, *Synlett* **2002**, 2098–2100.
- 34 A. N. Ajjou, H. Alper, *Macromolecules* **1996**, 29, 5072–5074.
- 35 A. N. Thadani, V. H. Rawal, *Org. Lett.* **2002**, 4, 4321–4323.
- 36 D. G. Miller, D. D. M. Wayner, *J. Org. Chem.* **1990**, 55, 2924–2927.
- 37 S. S. Stahl, *Angew. Chem. Int. Ed.* **2004**, 43, 3400–3420.
- 38 M. D. Bercich, R. C. Cambie, P. S. Rutledge, *Aust. J. Chem.* **1999**, 52, 241–257.
- 39 F. Derdar, J. Martin, C. Martin, J. M. Bregeault, J. Mercier, *J. Organomet. Chem.* **1988**, 338 (2), C21–C26.
- 40 A. Yamashita, A. Toy, T. A. Scahill, *J. Org. Chem.* **1989**, 54, 3625–3634.
- 41 B. Betzemeier, F. Lhermitte, P. Knochel, *Tetrahedron Lett.* **1998**, 39, 6667–6670.
- 42 M. Roussel, H. Mimoun, *J. Org. Chem.* **1980**, 45, 5387–5390.
- 43 A. K. Bose, L. Krishnan, D. R. Wagle, M. S. Manhas, *Tetrahedron Lett.* **1986**, 27, 5955–5958.
- 44 S.-K. Kang, K.-Y. Jung, J.-U. Chung, E.-Y. Namkoong, T.-H. Kim, *J. Org. Chem.* **1995**, 60, 4678–4679.
- 45 R. Stragies, S. Blechert, *J. Am. Chem. Soc.* **2000**, 122, 9584–9591.
- 46 J. Lai, X. Shi, L. Dai, *J. Org. Chem.* **1992**, 57, 3485–3487.
- 47 T.-L. Ho, M. H. Chang, C. Chen, *Tetrahedron Lett.* **2003**, 44, 6955–6957.
- 48 B. L. Feringa, *J. Chem. Soc., Chem. Commun.* **1986**, 909–910.
- 49 H. Takikawa, K. Isono, M. Sasaki, F. A. Macias, *Tetrahedron Lett.* **2003**, 44, 7023–7025.
- 50 E. Keinan, K. K. Seth, R. Lamed, *J. Am. Chem. Soc.* **1986**, 108, 3474–3480.
- 51 A. Fettes, E. M. Carreira, *J. Org. Chem.* **2003**, 68, 9274–9283.
- 52 H. Nagashima, K. Sato, J. Tsuji, *Tetrahedron* **1985**, 41, 5645–5651.
- 53 J. Tsuji, N. Nagashima, K. Hori, *Chem. Lett.* **1980**, 257–260.
- 54 H. Usuda, M. Kanai, M. Shibasaki, *Org. Lett.* **2002**, 4, 859–862.
- 55 M. Tanaka, H. Urata, T. Fuchikami, *Tetrahedron Lett.* **1986**, 27, 3165–3168.
- 56 A. I. Roshchin, S. M. Kel'chevski, N. A. Bumagin, *J. Organomet. Chem.* **1998**, 560, 163–167.
- 57 K. Matsui, S. Uchimumi, A. Iwayama, T. Umeza, to *Ube-Industries*, EP 55108, **1982**.
- 58 T. Hosokawa, T. Yamanaka, M. Itotani, S.-I. Murahashi, *J. Org. Chem.* **1995**, 60, 6159–6167.
- 59 P. Ambrosi, A. Arnone, P. Bravo, L. Bruché, A. De Cristofaro, V. Francardi, M. Frigerio, E. Gatti, G. S. Germinara, W. Panzeri, F. Pennacchio, C. Pesenti, G. Rotundo, P. F. Roversi, C. Salvadori, F. Viani, M. Zanda, *J. Org. Chem.* **2001**, 66, 8336–8343.

3

C–H Transformation at Aldehydes and Imines

3.1

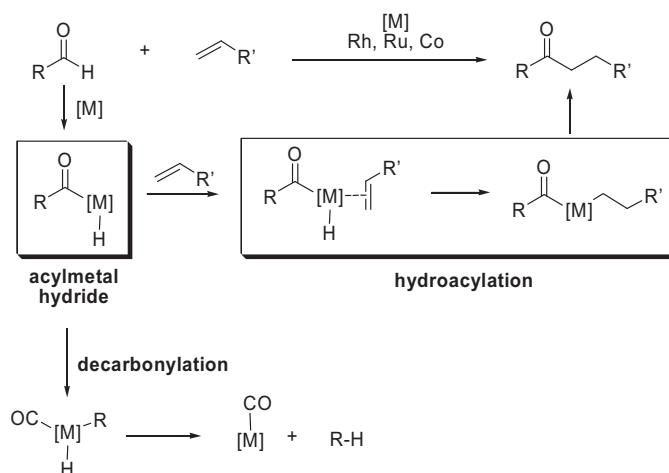
Inter- and Intramolecular Hydroacylation

Chul-Ho Jun and Young Jun Park

3.1.1

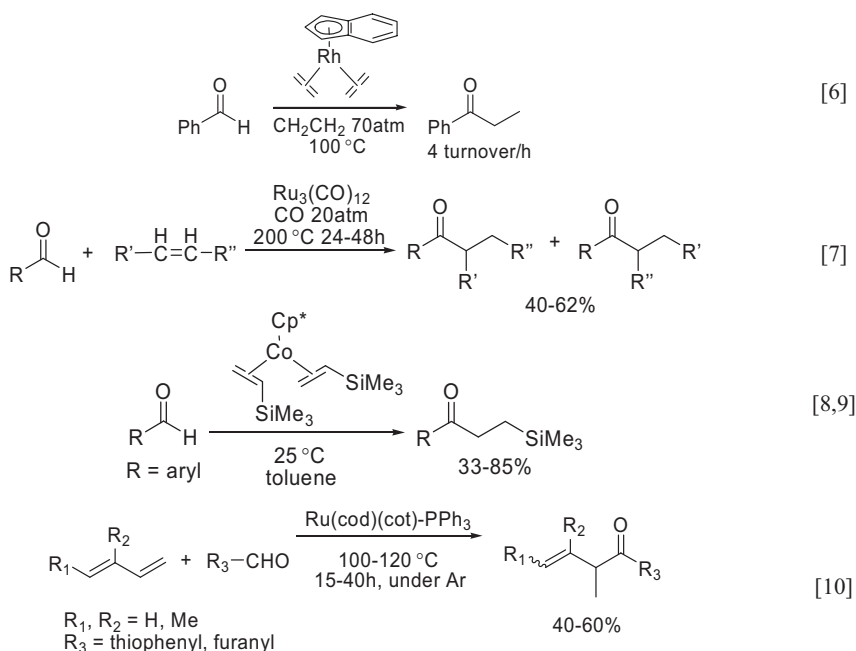
Introduction and Fundamental Examples

The hydroacylation of olefins with aldehydes is one of the most promising transformations using a transition metal-catalyzed C–H bond activation process [1–4]. It is, furthermore, a potentially environmentally-friendly reaction because the resulting ketones are made from the whole atoms of reactants (aldehydes and olefins), i.e. it is atom-economic [5]. A key intermediate in hydroacylation is a acyl metal hydride generated from the oxidative addition of a transition metal into the C–H bond of the aldehyde. This intermediate can undergo the hydrometalation of the olefin followed by reductive elimination to give a ketone or the undesired decarbonylation, driven by the stability of a metal carbonyl complex as outlined in Scheme 1.



Scheme 1. Hydroacylation vs. decarbonylation.

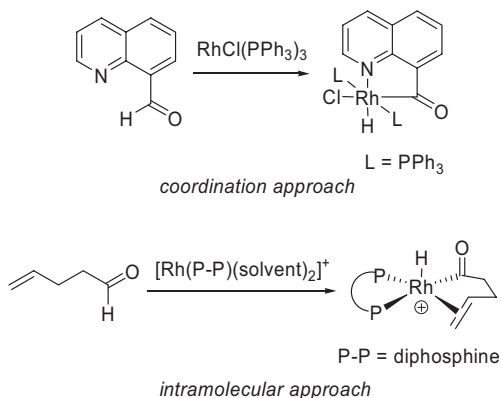
Suppression of the competitive decarbonylation reaction is essential to make the hydroacylation reaction predominant. For this reason, early intermolecular hydroacylation reactions required rather harsh conditions or specific reagents, leading to substrate limitation (Scheme 2) [6–10]. To circumvent this limitation, stabilization of the acyl metal hydride is required and two approaches, though they are conceptually identical (cyclometallation), exist [11, 12] –attachment of an additional coordinating group on the aldehyde to form a stable five-membered metalacycle [13], and placement of both aldehyde and olefin in a molecule to make a reaction proceed intramolecularly [14] (Scheme 3). The former strategy is usually used in intermolecular reactions and the latter in intramolecular reactions. In contrast with earlier examples which employ high temperatures and/or high pressures of carbon monoxide and ethylene, these approaches provide milder, more efficient, general and selective reaction environments.



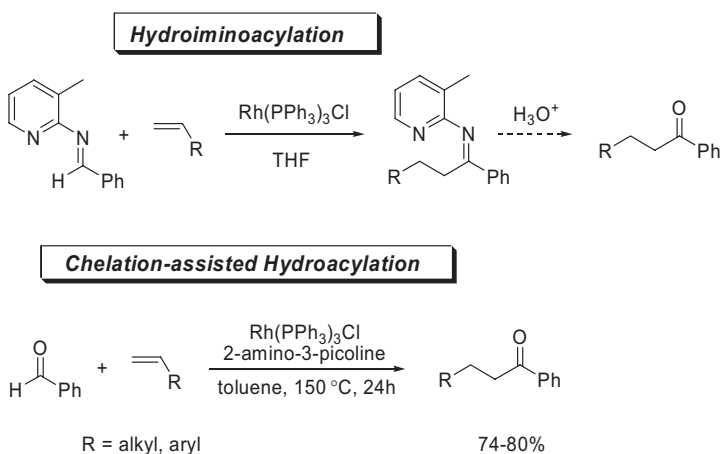
Scheme 2. Early examples.

An interesting example is the hydroiminoacylation reaction, a good alternative to hydroacylation reactions, using aldimines as a synthetic equivalent to aldehydes (Scheme 4) [4]. The rhodium-catalyzed hydroiminoacylation of an olefin with aldimines produced a ketimine which could be further acid-hydrolyzed to give the ketone. The reaction proceeded via the formation of a stable iminoacylrhodium(III) hydride (this will be discussed in the mechanism section), production of which is facilitated by initial coordination of the rhodium complex to the pyridine moiety of the aldimine. This hydroiminoacylation procedure opened up the direct

use of aldehydes as substrates for hydroacylation based on the in-situ generation of aldimines from the aldehyde and 2-amino-3-picoline, a reaction which was called chelation-assisted hydroacylation (Scheme 4).

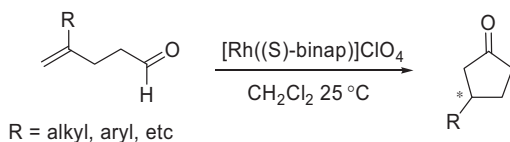


Scheme 3. Cyclometalation models.



Scheme 4. Hydroiminoacylation and chelation-assisted hydroacylation.

Intramolecular hydroacylation, on the other hand, is an attractive catalytic process because it produces cyclic ketones. Furthermore, with appropriate chiral phosphine ligands, this reaction could convert prochiral 4-pentenals into chiral cyclopentanones (Scheme 5) [14].

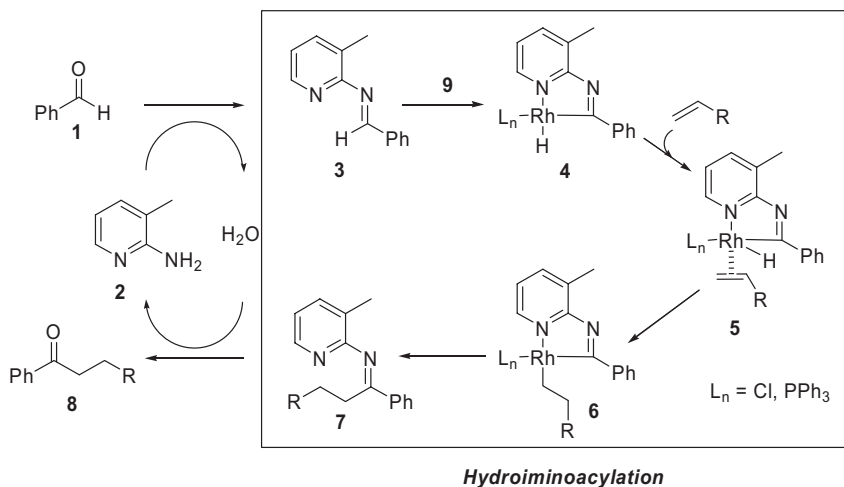


Scheme 5. Intramolecular hydroacylation.

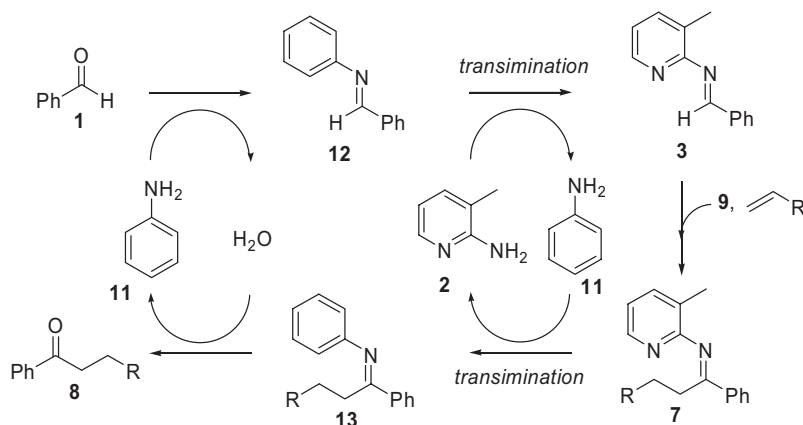
3.1.2

Mechanism

Since the decarbonylation of aldehydes by Wilkinson's complex, $\text{Rh}(\text{PPh}_3)_3\text{Cl}$ (**9**), was discovered, the formation of acylmetal hydride species by oxidative addition of aldehydic C–H bonds to transition metals is a key intermediate in hydroacylation reactions [15, 16]. Iminohydroacylation reactions also involve similar iminoacylmetal intermediates. First, benzaldehyde condenses with **2** to form aldimine **3**, which then undergoes hydroiminoacylation to afford ketimine **7**, via formation of acylrhodium(III) hydride **4**, then hydrometalation of the olefin to form **6** and reductive elimination. Because the ketimine is more susceptible than the aldimine toward hydrolysis, it is readily hydrolyzed to ketone **8** by water generated during the condensation step, thus regenerating **2** (Scheme 6). Therefore, amine **2** is used as a catalyst to assist chelation with the rhodium complex. In fact, in the absence of **2**, no hydroacylation occurred and aldehydes underwent the rapid decarbonylation. In this mechanism, the imine condensation step is rate determining, because whole reactions could be dramatically accelerated by acid catalysis and the transimination reaction. Thus, a very efficient catalyst, which consists of **9**, **2**, benzoic acid (**10**), and aniline (**11**) was developed. With this catalytic system the reaction time could be reduced from 24 h to 1 h even at 130 °C [17]. The mechanism of this reaction is depicted in Scheme 7. Initially, an aldehyde condenses with a more reactive aniline to form aldimine **12**. Subsequent transimination with **2** generates **3** which participates in hydroiminoacylation of an olefin. The high reactivity of this catalyst system implies that the condensation of an aldehyde with **11** followed by transimination of **12** into **3** is more facile than direct condensation of the aldehyde with **2**.

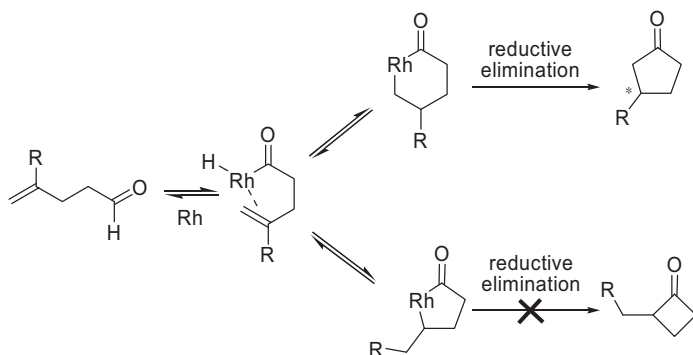


Scheme 6. Mechanism of hydroiminoacylation.



Scheme 7. Mechanism of hydroiminoacylation by transimination.

In the intramolecular hydroacylation, on the other hand, the choice of catalyst is important. As in the intermolecular hydroacylation, Wilkinson's catalyst **9** and its analog could not promote intramolecular hydroacylation efficiently because catalytically inactive rhodium carbonyl complexes form rapidly. Thus, cationic species and chelate phosphines are usually needed to prevent the decarbonylation process, as in Scheme 3 [14]. The efficiency of the catalyst is related to the rapid displacement of the solvent molecules and to the availability of at least three vacant coordination sites on the catalyst for the hydride, acyl, and olefin ligands. In the Rh(I)-catalyzed intramolecular hydroacylation of 4-alkenal derivatives, both five- and six-membered metallacycles have been generated during the reaction, although the six-membered metallacycle selectively produces the cyclopentanone (Scheme 8). The main origin of chiral induction is expected to arise from the spatial arrangements of alkyl or aryl groups at the phosphorous atom and the chiral configuration is determined by the chirality of the chelating ring.



Scheme 8. Mechanism of intramolecular hydroacylation.

Table 1. Examples for inter- and intramolecular hydroacylation.

Substrate	Product	Catalytic system	Ref.
	71-99%	Rh(PPh ₃) ₃ Cl 2-amino-3-picoline Aniline, benzoic acid	[17]
	22-86%	RhCl ₃ · xH ₂ O PPh ₃ 2-amino-4-picoline	[18]
	70-96%	Rh(PPh ₃) ₃ Cl 2-amino-3-picoline	[19]
	76-96%	Rh(PPh ₃) ₃ Cl 2-amino-3-picoline Benzoic acid	[20]
	100% (iso/normal=4/1)	Rh(PPh ₃) ₃ Cl	[21]
	33-84%	[Rh(dppe)]ClO ₄	[22]
	65%	[Rh(dppe)]ClO ₄ Ethylene	[23]
	high ee >90%	[Rh(chiral P-P)]ClO ₄	[14]
	67-88%	[Rh(dppe)] ₂ (BF ₄) ₂	[24]
	62% 13% 6%	[Rh(dppe)]ClO ₄	[25]

3.1.3

Scope and Limitations

A primary alcohol and amines can be used as an aldehyde precursor, because it can be oxidized by transfer hydrogenation. For example, the reaction of benzyl alcohol with excess olefin afforded the corresponding ketone in good yield in the presence of Rh complex and 2-amino-4-picoline [18]. Similarly, primary amines, which were transformed into imines by dehydrogenation, were also employed as a substrate instead of aldehydes [19]. Although various terminal olefins, alkynes [20], and even dienes [21] have been commonly used as a reaction partner in hydroiminoacylation reactions, internal olefins were ineffective. Recently, methyl sulfide-substituted aldehydes were successfully applied to the intermolecular hydroacylation reaction [22]. Also in the intramolecular hydroacylation, extension of substrates such as cyclopropane-substituted 4-enal [23], 4-alkynal [24], and 4,6-dienal [25] has been developed (Table 1).

Experimental**Heptanophenone by Hydroiminoacylation**

A screw-capped pressure vial (1 mL) was charged with freshly purified benzaldehyde (0.5 mmol), 2-amino-3-picoline (0.1 mmol), benzoic acid (0.03 mmol), aniline (0.3 mmol), 1-hexene (2.5 mmol), and toluene (80 mg). After stirring the mixture at room temperature for some minutes, $[(PPh_3)_3RhCl]$ (0.01 mmol) was added and the mixture was then stirred in an oil bath preheated to 130 °C for 1 h. After cooling to room temperature, the reaction mixture was purified by column chromatography (SiO_2 , *n*-hexane–ethyl acetate, 4:1) to yield pure heptanophenone (0.49 mmol, 98 % yield).

3.2

Cyclization of Aldehydes and Imines via Organopalladium Intermediates

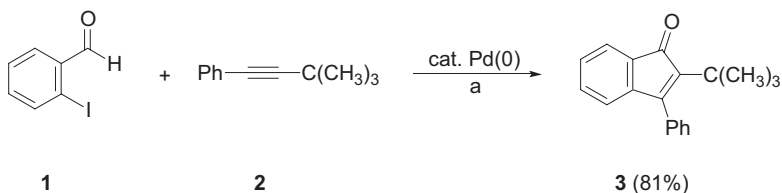
Xiaoxia Zhang and Richard C. Larock

3.2.1

Introduction

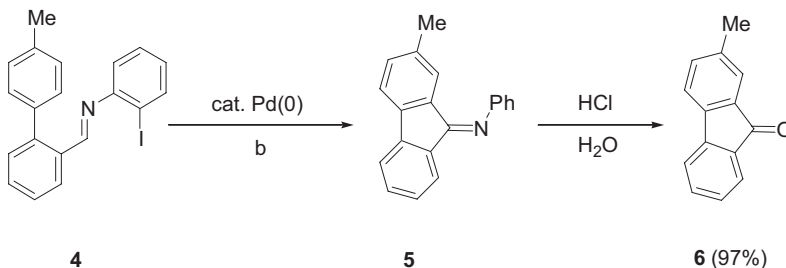
Palladium reagents have been used extensively to prepare various carbo- and heterocyclic compounds by cyclic carbopalladation and annulation [1]. One of the most important factors contributing to the widespread application of palladium catalysts in organic synthesis is their tolerance of most important organic functional groups, i.e. aldehydes, ketones, imines, carboxylic acids, and their derivatives are usually readily accommodated by organopalladium intermediates under conditions in which carbon–carbon bond formation is facile [2]. Under some reaction conditions, however, organopalladium intermediates undergo several intramolecular C–H activation reactions with aldehydes and imines that they would

not normally undergo if the reaction were intermolecular. For example, the palladium-catalyzed reaction of *o*-iodo- or *o*-bromobenzaldehyde with internal alkynes has proven to be an effective method for synthesis of indenones [3]. The key ring-closure step involves the C–H transformation of an aldehyde (Scheme 1).



Scheme 1. C–H transformation of aldehydes: (a) 5 mol% Pd(OAc)₂, 4 equiv. Na₂CO₃, 1 equiv. *n*-Bu₄NCl, DMA, 100 °C, 24 h.

The C–H transformation of imines via palladacycles has recently provided a novel synthesis of fluoren-9-ones [4]. This high yielding synthesis is achieved by migration of palladium from an aryl position to an imidoyl position via C–H activation of the imine moiety, followed by intramolecular arylation (Scheme 2).



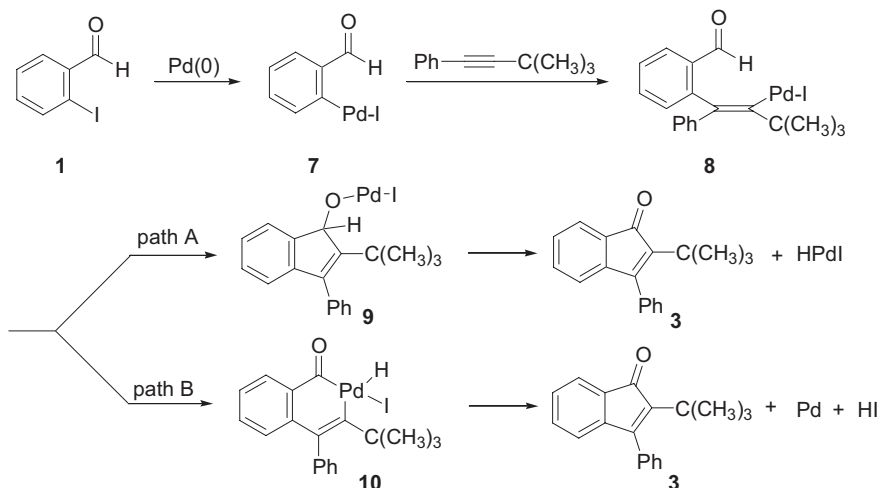
Scheme 2. C–H transformation of imines: (b) 5 mol% Pd(OAc)₂, 5 mol% (Ph₃P)₂CH₂, 2 equiv. CsO₂CCMe₃, DMF, 100 °C, 4 h.

3.2.2

Mechanism

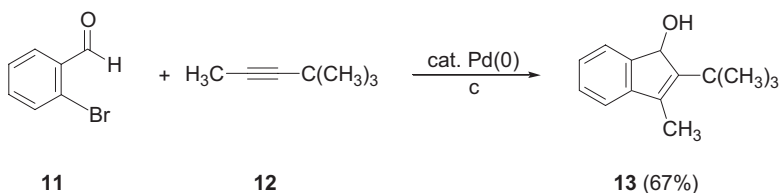
The mechanism of the indenone synthesis (Scheme 3) seems to involve: (1) oxidative addition of the aryl iodide to Pd(0); (2) arylpalladium coordination to the alkyne and subsequent insertion of the alkyne to form a vinylpalladium intermediate (**8**), (3) then either the vinylic palladium intermediate adds to the carbonyl group and subsequently undergoes a β-hydride elimination (path A) or the aldehydic C–H bond may oxidatively add to the palladium to produce an organopalladium(IV) intermediate (six-membered ring palladacycle) which subsequently undergoes rapid reductive elimination of the indenone and palladium (path B). The actual mode of ring closure of the vinylic palladium intermediate to the inde-

none is unclear. Overall, the C–H bond of the aldehyde is transformed into a new C–C bond.



Scheme 3. Mechanism of the synthesis of indenones **3**.

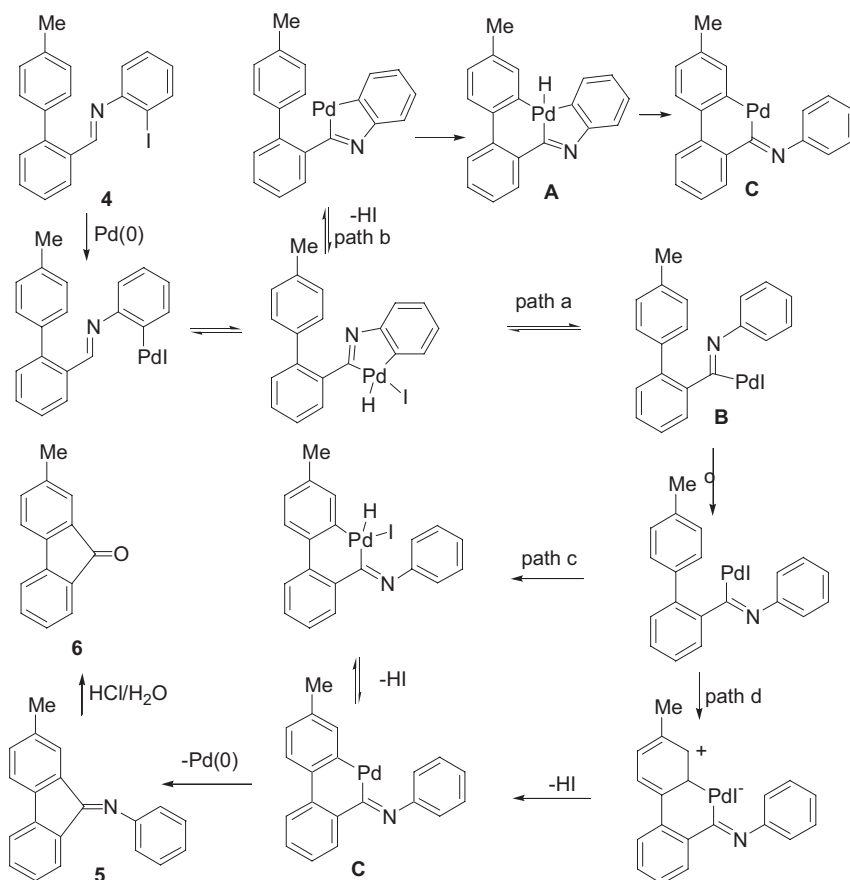
Yamamoto et al. have reported that reaction of internal alkynes with *o*-bromo-benzaldehydes [5] or analogous ketones [6] under different reaction conditions affords indenols (Scheme 4). It is believed the mechanism is similar to that of Scheme 3, but using path A, except that the protonolysis of intermediate **9** in Scheme 3 occurs, rather than β -hydride elimination, to form indenols. Therefore, no C–H bond transformation is involved in this indenol process.



Scheme 4. Synthesis of indenols by nucleophilic attack of a vinylic palladium species on a carbonyl: (c) 5 mol% Pd(OAc)₂, 2 equiv. KOAc, 10 equiv. EtOH, DMF, 60 °C, 24 h.

It appears that the biarylcarboxaldehyde imine **4** affords *N*-fluoren-9-ylideneaniline **5** via the following mechanistic steps (Scheme 5). After oxidative addition of the C–I bond to Pd(0), the palladium undergoes a 1,4-palladium migration from the *ortho* position of the aniline to the imidoyl position (through path a), followed by arylation at the 2' position of the biaryl to generate the desired migration/arylation product **5**. Alternatively, the palladium intermediate may undergo what seems to be a rather unfavorable process (path b) to generate a highly strained

complex **A**, which after two reductive eliminations affords the final migration product. The high yield suggests that the palladium intermediate did, in fact, migrate from the aryl position to the imidoyl position by a complete through-space 1,4-shift to generate the imidoypalladium intermediate **B**. The imidoypalladium intermediate **B** apparently then undergoes either an insertion into the C–H bond of the neighboring arene (path c) or electrophilic aromatic substitution (path d). After elimination of HI, both pathways give a six-membered ring palladacycle **C**. Subsequent reductive elimination and hydrolysis then afford the observed ketone product **6**.



Scheme 5. Mechanistic pathway for C–H activation of imines: synthesis of fluoren-9-ones.

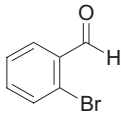
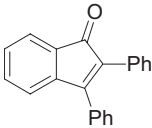
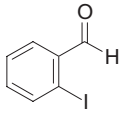
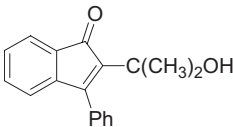
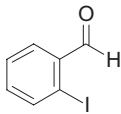
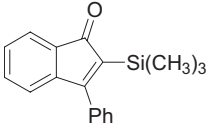
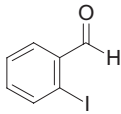
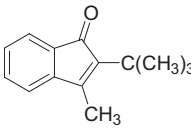
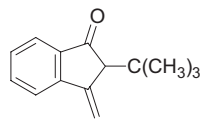
3.2.3

Scope and Limitations

o-Iodobenzaldehydes usually give modest to good yields of indenones by the process shown in Scheme 1. *o*-Bromobenzaldehydes can also be employed successfully in this annulation process, although in a slightly lower yield, and longer reac-

tion times are needed (Table 1, entry 1). This process is reasonably general for diaryl, dialkyl, and aryl-alkyl internal alkynes providing indenones with a variety of substituents in the 2 and 3 positions (Table 1, entries 2–4). Hydroxy and silyl groups are accommodated (Table 1, entries 2 and 3). Isomerization of some of the products to β,γ -enones is observed with indenones bearing a primary alkyl group in the 3-position (Table 1, entry 4). The ease of isomerization is attributed to the antiaromaticity of the indenone ring system.

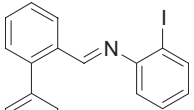
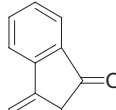
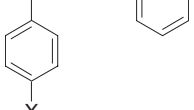
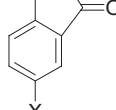
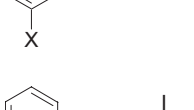
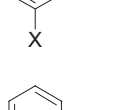
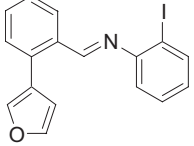
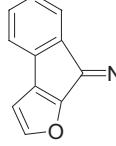
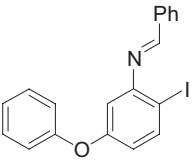
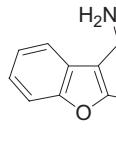
Table 1. Examples of C–H transformations of aldehydes: synthesis of indenones.

Entry	Benzaldehyde	Alkyne	Product(s)	Yield (%)
1		$\text{Ph} \equiv \text{Ph}$		82
	11	14	15	
2		$\text{Ph} \equiv \text{C}(\text{CH}_3)_2\text{OH}$		58
	1	16	17	
3		$\text{Ph} \equiv \text{Si}(\text{CH}_3)_3$		42
	1	18	19	
4		$\text{H}_3\text{C} \equiv \text{C}(\text{CH}_3)_3$	 + 	26 + 26
	1	12	20 21	

The C–H transformation reactions of biarylcarboxaldehyde imines bearing different functional groups on the aromatic rings has been investigated. Electron-donating groups, for example methoxy groups, on the biaryl facilitate the arylation step and reduce the reaction time to 2 h (Table 2, entry 2). Although the presence of an electron-withdrawing group, for example a nitro group, on the ring under-

going substitution makes the aromatic ring more electron-deficient, and therefore makes electrophilic aromatic substitution more difficult, electron-withdrawing groups do not affect the overall yield, although substantially longer reaction times are required (Table 2, entry 3). After 1,4-migration of the palladium from the aryl to the imidoyl position, subsequent substitution of a furan also proceeds smoothly (Table 2, entry 4). The substrate with the electron-rich furan moiety requires a shorter reaction time. Migration of the palladium in the imidoypalladium intermediate to another aryl position before trapping is also possible, although a higher temperature and much longer reaction time are required and the yield is lower (Table 2, entry 5). The reluctance of the palladium in this imidoypalladium species to migrate to the sterically hindered *ortho* position of the phenoxy group might account for these observations.

Table 2. Synthesis of fluorenones via 1,4-palladium migration and subsequent arylation of imines.

Entry	Imines	Time (h)	Product	Yield (%)
1	 X = Me 4	4		6 97
2	 X = OMe 22	2		23 100
3	 X = NO ₂ 24	12		25 100
4	 26	2		27 82
5	 28	168		29 35

Experimental

2-*tert*-Butyl-3-phenyl-1-indenone (**3**)

Pd(OAc)₂ (6 mg, 0.027 mmol), Na₂CO₃ (212 mg, 2.0 mmol), *n*-Bu₄NCl (150 mg, 0.54 mmol), 2-iodobenzaldehyde (116 mg, 0.5 mmol), *tert*-butylphenylacetylene (158 mg, 1.0 mmol), and 10 mL DMA were placed in a 4-dram vial which was

heated in an oil bath at 100 °C for 24 h. The reaction was monitored by TLC to establish completion. The reaction mixture was cooled, diluted with 30 mL ether, washed with saturated NH_4Cl solution (2×45 mL), dried over anhydrous Na_2SO_4 , and filtered. The solvent was evaporated under reduced pressure. The reaction mixture was chromatographed using 15:1 hexane–EtOAc to yield a yellow solid (mp 114–116 °C, from *n*-hexane): ^1H NMR (CDCl_3) δ 1.16 (s, 9 H, CH_3), 6.47 (d, $J = 7.2$ Hz, 1 H, aryl), 7.0–7.6 (m, 8 H, aryl); ^{13}C NMR (CDCl_3) δ 30.6, 33.6, 120.3, 121.7, 127.8, 128.03, 128.08, 128.1, 129.8, 133.3, 135.3, 141.4, 147.6, 153.9, 198.4; IR (CHCl_3) 1699 ($\text{C}=\text{O}$) cm^{-1} ; mass spectrum m/z 262.13617 (calcd for $\text{C}_{19}\text{H}_{18}\text{O}$, 262.13577).

2-Methylfluoren-9-one (6)

The *N*-(4'-methylbiphenyl-2-ylmethylene)-2-iodoaniline (0.25 mmol), $\text{Pd}(\text{OAc})_2$ (2.8 mg, 0.0125 mmol), *bis*(diphenylphosphino)methane (dppm; 4.8 mg, 0.0125 mmol), and $\text{CsO}_2\text{CCMe}_3$ (0.117 g, 0.5 mmol) in DMF (4 mL) under Ar were heated at 100 °C with stirring for 4 h. The reaction mixture was then cooled to room temperature, diluted with diethyl ether (35 mL), and washed with brine (30 mL). The aqueous layer was re-extracted with diethyl ether (15 mL). The combined organic layers were dried over MgSO_4 , filtered, and the solvent was removed to afford the crude imine product. To an acetone (5 mL) solution of the crude imine product, 1.0 M HCl (2 mL) was added. The resulting reaction mixture was stirred until disappearance of the imine was indicated by thin layer chromatography. The mixture was then diluted with H_2O and extracted with diethyl ether (2×15 mL). The organic extract was dried over MgSO_4 , filtered, and the solvent was removed under reduced pressure to afford the crude fluoren-9-one, which was purified by flash chromatography using 7:1 hexanes–ethyl acetate to afford a yellow solid: m.p. 90–91 °C (lit. [7] m.p. 92 °C); ^1H NMR (CDCl_3) δ 2.33 (s, 3H), 7.19–7.24 (m, 2H), 7.33 (d, $J = 7.6$ Hz, 1H), 7.04–7.41 (m, 3H), 7.58 (d, $J = 7.2$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 21.4, 120.0, 120.2, 124.2, 125.0, 128.6, 134.3, 134.4, 134.7, 135.1, 139.3, 141.8, 144.7, 194.2. The spectral properties were identical with those previously reported [7].

References to Chapter 3 – C–H Transformation at Aldehydes and Imines

References and Notes to Section 3.1

- 1 G. Dyker, *Angew. Chem. Int. Ed.* **1999**, 38, 1699–1712.
- 2 J. A. Labinger, J. E. Bercaw, *Nature* **2002**, 417, 507–514.
- 3 V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev.* **2002**, 102, 1731–1769.
- 4 C.-H. Jun, C. W. Moon, D.-Y. Lee, *Chem. Eur. J.* **2002**, 8, 2423–2428.
- 5 B. M. Trost, *Acc. Chem. Res.* **2002**, 35, 695–705.
- 6 T. B. Marder, D. C. Roe, D. Milstein, *Organomet.* **1988**, 7, 1451–1453.
- 7 T. Kondo, M. Akazome, Y. Tsuji, Y. Watanabe, *J. Org. Chem.* **1990**, 55, 1286–1291.
- 8 C. P. Lenges, M. Brookhart, *J. Am. Chem. Soc.* **1997**, 119, 3165–3166.
- 9 C. P. Lenges, P. S. White, M. Brookhart, *J. Am. Chem. Soc.* **1998**, 120, 6965–6979.
- 10 T. Kondo, N. Hiraishi, Y. Morisaki, K. Wada, Y. Watanabe, T. Mitsudo, *Organomet.* **1998**, 17, 2131–2134.
- 11 B. Breit, *Chem. Eur. J.* **2000**, 6, 1519–1524.
- 12 M. I. Bruce, *Angew. Chem. Int. Ed.* **1977**, 16, 73.
- 13 J. W. Suggs, *J. Am. Chem. Soc.* **1978**, 100, 640–641.
- 14 B. Bosnich, *Acc. Chem. Res.* **1998**, 31, 667–674.
- 15 C. F. Lochow, R. G. Miller, *J. Am. Chem. Soc.* **1976**, 98, 1281–1283.
- 16 J. Tsuji, K. Ohno, *J. Am. Chem. Soc.* **1968**, 90, 94.
- 17 C.-H. Jun, D.-Y. Lee, H. Lee, J.-B. Hong, *Angew. Chem. Int. Ed.* **2000**, 39, 3070.
- 18 C.-H. Jun, C.-W. Huh, S.-J. Na, *Angew. Chem. Int. Ed.* **1998**, 37, 145–147.
- 19 C.-H. Jun, K.-Y. Chung, J.-B. Hong, *Org. Lett.* **2001**, 3, 785–787.
- 20 C.-H. Jun, H. Lee, J.-B. Hong, B.-I. Kwon, *Angew. Chem. Int. Ed.* **2002**, 41, 2146–2147.
- 21 M. Tanaka, M. Imai, Y. Yamamoto, K. Tanaka, M. Shimowatari, S. Nagumo, N. Kawahara, H. Suemune, *Org. Lett.* **2003**, 5, 1365–1367.
- 22 M. C. Willis, S. J. McNally, P. J. Beswick, *Angew. Chem. Int. Ed.* **2004**, 43, 340–343.
- 23 A. D. Aloise, M. E. Layton, M. D. Shair, *J. Am. Chem. Soc.* **2000**, 122, 12610–12611.
- 24 K. Tanaka, G. C. Fu, *J. Am. Chem. Soc.* **2001**, 123, 11492–11493.
- 25 Y. Sato, Y. Oonishi, M. Mori, *Angew. Chem. Int. Ed.* **2002**, 41, 1218–1221.

References to Section 3.2

- 1 (a) Negishi, E.; Copéret, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, 96, 365; (b) Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*, Pergamon: Oxford, 2000; (c) Bäckvall, J.-E. *Pure Appl. Chem.* **1992**, 64, 429; (d) Larock, R. C. *J. Organomet. Chem.* **1999**, 576, 111; (e) Collins, I. J. *Chem. Soc., Perkin Trans. 1* **2000**, 2845.
- 2 (a) Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*, John Wiley: Chichester, U.K., 1995; (b) Soderberg, B. C. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 12, p 241.
- 3 Larock, R. C.; Doty, M. J.; Cacchi, S. *J. Org. Chem.* **1993**, 58, 4579.
- 4 Yue, D.; Larock, R. C., work in progress.
- 5 Gevorgyan, V.; Quan, L. G.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, 40, 4089.
- 6 Quan, L. G.; Gevorgyan, V.; Yamamoto, Y. *J. Am. Chem. Soc.* **1999**, 121, 3545.
- 7 Campo, M. A.; Larock, R. C. *J. Org. Chem.* **2002**, 67, 5616.

IV

C–H Transformation at sp^3 -hybridized Carbon Atoms

1

C–H Transformation at Functionalized Alkanes

1.1

C–H Transformation in the Position α to Polar Functional Groups

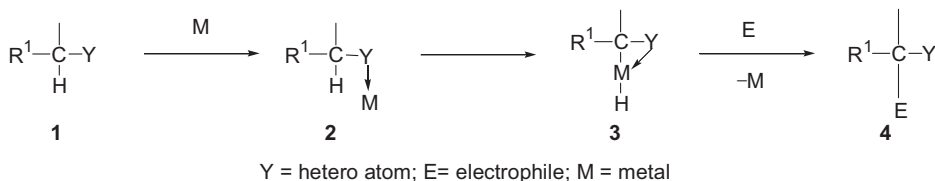
1.1.1

Transition Metal-catalyzed C–H Activation of Pronucleophiles
by the α -Heteroatom Effect*Shun-Ichi Murahashi*

1.1.1.1 Introduction

C–H activation with transition-metal complexes will open a new chemistry of catalytic carbon–carbon bond formation because of its potent ability to generate reactive carbon–metal complexes. The design of a catalytic reaction which involves C–H activation followed by reaction with a reagent such as an electrophile is particularly important to provide an environmentally friendly non-salt process, which proceeds under neutral conditions.

sp^3 C–H activation with transition-metal complexes [1, 2] is difficult in comparison with sp and sp^2 C–H activation [3], because the reactivity of the C–H bond towards metals depends on the magnitude of the s-character of carbons [1, 2]. For activation of an sp^3 C–H bond, there may be several approaches, which include (1) oxidative addition of transition metals to the sp^3 C–H bonds, (2) hydrogen abstraction by metal oxo species and related active species [4], (3) activation of α -C–H bonds adjacent to heteroatoms using the α -heteroatom effect [1, 2, 5]. The last concept is depicted in Scheme 1. Coordination of the heteroatom (Y) of substrate (1) to low-valent-transition metal (M) would increase both the basicity of the metal and the acidity of the C–H bond adjacent to Y, resulting in oxidative addition of

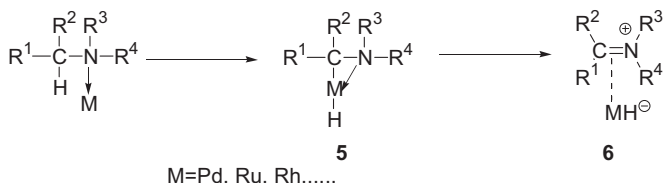


Scheme 1. sp^3 C–H activation by the α -heteroatom effect.

the metal into the α -C–H bond to give an α -metalated intermediate (3), which undergoes reaction with various reagents to give the product 4.

1.1.1.2 The C–H Activation of Tertiary Amines

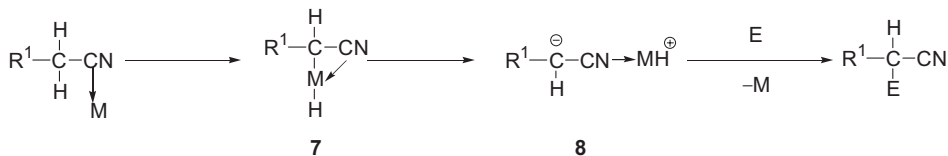
In 1978, Murahashi et al. discovered the C–H activation of tertiary amines [6]. The C–H activation occurs on treatment of any kind of low-valent transition metal or metal complex as shown in Scheme 2. Coordination of the metal or metal complex to the nitrogen of tertiary amines (5), followed by oxidative addition at the α -C–H bond gives an iminium ion complex (6), which is a useful intermediate for catalytic transformations of tertiary amines. Typically, the catalytic alkyl group-exchange reaction of tertiary amines [6] and hydrolysis reaction of tertiary amines [7] are performed highly efficiently. The C–H activation of tertiary amines has been proved by (1) d-labeling experiments at the α - and β -positions, (2) racemization of the optically active amines, (3) product analysis [5, 6], although at that time the concept of C–H activation was quite rare. This concept for the C–H activation of tertiary amines by the α -hetero atom effect led to new methods for activation of various organic substrates bearing hetero atom such as nitriles, carbonyl compounds, isocyanides under neutral conditions.



Scheme 2. The C–H activation of tertiary amines.

1.1.1.3 The C–H Activation of Nitriles

The concept has been extended to the C–H activation of nitriles, which coordinate strongly with metals. As shown in Scheme 3, coordination of a nitrile to low-valent metal complex (M) would increase both the basicity of the metal complex and the acidity of the C–H bond adjacent to the nitrile, and hence oxidative addition of the metal into the α -C–H bond of the nitrile would occur readily to afford an α -cyanoalkyl metal hydride complex (7), which undergoes isomerization to a N-bonded nitrile complex (8). The reaction of 8 with an C-electrophile forms a carbon–carbon



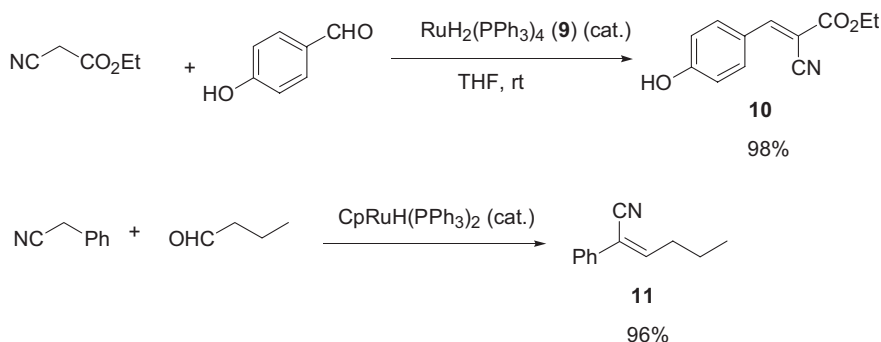
M = Ru, Pd, Rh, Ir, Re,

Scheme 3. The C–H activation of nitriles.

bon bond at the α -position of nitrile under neutral conditions. In 1989, Murahashi et al. discovered that the C–H activation of nitriles occurs readily on treatment with a catalyst such as $\text{RuH}_2(\text{PPh}_3)_4$ (**9**) [8]. Initiated by C–H activation, nitriles undergo various catalytic reactions, which include Aldol type reactions, Knoevenagel reactions, Michael addition, addition to acetylenes, and addition to imines, highly efficiently under neutral and mild conditions [1, 2].

1.1.1.4 Aldol Type Reactions and Knoevenagel Reactions of Nitriles

The reaction of nitriles with aldehydes in the presence of the catalyst **9** proceeds under neutral conditions to give the corresponding α,β -unsaturated nitriles [8]. It is noteworthy that even acidic substrates tolerate the reaction. Thus, the reaction of ethyl cyanoacetate with 4-hydroxybenzaldehyde gave ethyl (*E*)-2-cyano-3-(4-hydroxyphenyl)-2-propenoate (**10**) in 98 % yield [7, 8].



Scheme 4. The ruthenium-catalyzed aldol-type condensation and Knoevenagel reaction.

Ruthenium catalysts bearing electron-donating ligands, for example $\text{RuCpH}(\text{PPh}_3)_2$ and $\text{RuCp}^*\text{H}(\text{PPh}_3)_2$, would have higher reactivity for the C–H activation of nitriles. Thus, in the presence of catalyst $\text{RuHCp}(\text{PPh}_3)_2$, the condensation of less reactive phenylacetonitrile with butanal gives (*Z*)-2-phenyl-2-hexenenitrile (**11**) in 96 % yield [9]. It is noteworthy that after discovery of the reactions with catalyst **9** [9], Knoevenagel condensation of nitriles has been found to occur with various catalysts such as $\text{RuH}(\text{C}_2\text{H}_4)(\text{PPh}_3)_2(\text{C}_6\text{H}_4\text{PPh}_2)$ [10], $\text{RuCpH}(\text{PPh}_3)_2$ [9], $\text{RhH}(\text{CO})(\text{PPh}_3)_3$, [11] $\text{IrH}_5(\text{P-}i\text{-Pr}_3)_2$ [12], $\text{ReH}(\text{N}_2)(\text{PMe}_2\text{Ph})_4$ [13], and even heterogeneous catalysts such as ruthenium(II) immobilized on calcium hydroxyapatite [14].

1.1.1.5 Addition of Nitriles to Carbon–Carbon (Michael Addition) and Carbon–Nitrogen Multiple Bonds

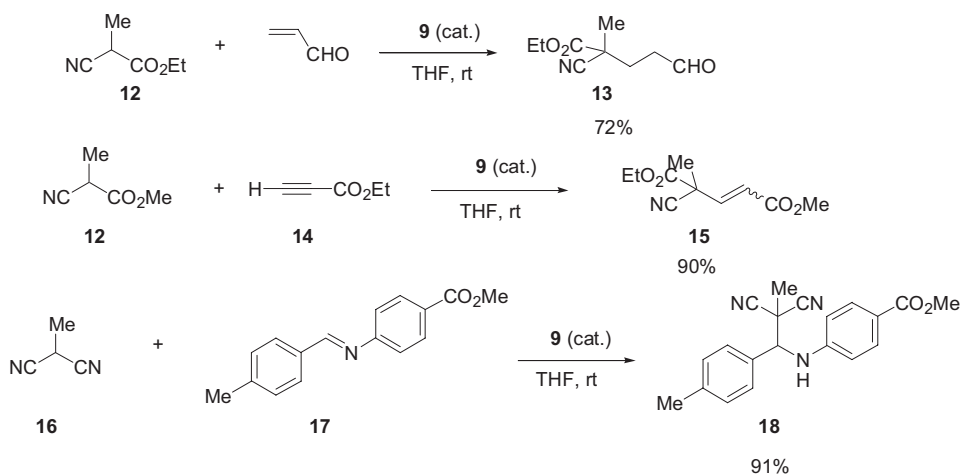
Using catalyst **9**, Michael reaction of nitriles can be also performed highly efficiently under neutral conditions. Addition of ethyl 2-cyanopropanoate (**12**) to 2-propanal proceeds chemoselectively to give the adduct **13** without contamina-

tion on the condensation product of the aldehyde, which is often observed by using conventional base [7, 8]. An important feature of the reaction is that the chemoselective C–H activation of nitriles occurs in the presence of C–H bond of other reactive substrates. Typically, the ruthenium-catalyzed reaction of an equimolar mixture of ethyl cyanoacetate and 2,4-pentanedione with benzaldehyde gave (*E*)-ethyl 2-cyano-3-phenyl-2-propenoate exclusively, although both pronucleophiles have similar pK_a values ($pK_a = 13$ in DMSO). In contrast, the same reaction in the presence of conventional bases such as AcONH_4 and KOH gave a thermodynamic mixture of (*E*)-ethyl 2-cyano-3-phenyl-2-propenoate and 3-benzylidene-2,4-pentanedione (75:25) [8].

The efficiency of this method is highlighted by highly diastereoselective Michael addition arising from specific chelation control by metals. Using the concept of these catalytic reactions, asymmetric carbon–carbon bond-formation can be performed. Reactions of isopropyl 2-cyanopropionate with vinyl ketones were conducted highly enantioselectively in the presence of $\text{RhH}(\text{CO})(\text{PPh}_3)_3$ with (*S,S*)-(*R,R*)-TRAP [14] ($\text{R} = \text{C}_6\text{H}_4$ -*p*-OMe; 99 %, 89 % ee) [15].

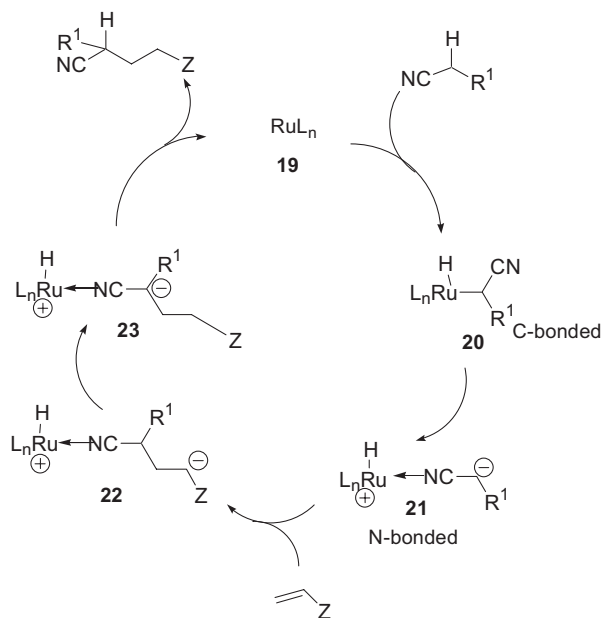
Addition of nitriles to acetylenic compounds proceeds with chemoselectivity in contrast with the corresponding base-promoted reactions, where the products derived from acetylides are contaminants. The $\text{RuH}_2(\text{PPh}_3)_4$ -catalyzed reaction of ethyl 2-cyanopropionate (**12**) with methyl propiolate (**14**) at room temperature gave **15** in 90 % yield.

The principle can be also applied to the addition of nitriles to imines. The reaction of 2-methylmalononitrile (**16**) with 4-methoxycarbonyl-*N*-(4-methylbenzylidene)aniline (**17**) in the presence of **1** [8] or $\text{RhH}(\text{CO})(\text{PPh}_3)_3$ (**15**) [16] gave the corresponding cyano amine **18** in 91 % yield.



Scheme 5. Catalytic Michael Addition of nitrile and addition of nitriles to acetylenes and imines.

The catalytic reaction can be rationalized by assuming the mechanism shown in Scheme 6 [2, 8, 18].



Scheme 6. The mechanism of Michael addition of nitriles.

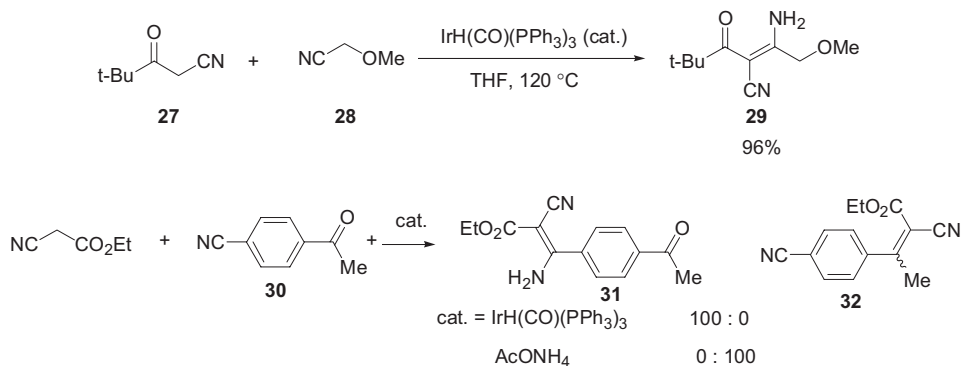
The catalytically active species seems to be the low-valent ruthenium complex RuL_n (**19**). Coordination of nitrile to **19**, subsequent oxidative addition of the ruthenium to the α -C–H bond of nitrile would afford the α -cyanoalkylruthenium hydride complex **20** (C-bonded complex), which is converted to the hydrido(enolato)ruthenium complex **21** (N-bonded complex). The intermediacy of **21** has been confirmed by isolation of $\text{Ru}^+\text{H}(\text{NCC}-\text{HCO}_2\text{Et})(\text{NCCH}_2\text{CO}_2\text{Et})(\text{PPh}_3)_3$ (**24**) from the reactions of ethyl cyanoacetate with either $\text{RuH}(\text{C}_2\text{H}_4)(\text{PPh}_3)_2(\text{PPh}_2\text{C}_6\text{H}_4)$ or **9** [8]. The complex **24**, which is a catalyst for above reactions, was unequivocally characterized by X-ray structural analysis [8, 10]. Furthermore the corresponding C-bonded complex, $\text{RuCp}[\text{CH}(\text{CN})\text{SO}_2\text{Ph}](\text{PPh}_3)_3$ (**25**) and N-bonded complex, $\text{Ru}^+\text{Cp}(\text{NCCH}^-\text{SO}_2\text{Ph})(\text{PR}_3)_2$ (**26**) could be isolated, and their structures were determined by X-ray analysis [17]. The isomerization of **25** to **26** was also observed, and this depends on the cone angle of the phosphine ligand [17, 18]. The reaction of the enolato ligand of **21** with an alkene gives hydrido(aldolato)ruthenium intermediate **22**, which undergoes isomerization to give **23**, and subsequent reductive elimination gives the product [8, 19].

1.1.1.6 Catalytic Thorpe–Ziegler reaction (Addition of Nitriles to Nitriles)

It has been found that low-valent iridium hydride complexes are effective catalysts for activation of both the α -C–H bond and the CN triple bond of nitrile. Actually, the catalytic cross condensation of nitrile **27** and nitrile **28** in the presence of $\text{IrH}(\text{CO})(\text{PPh}_3)_3$ catalyst (**29**) was performed under neutral conditions to give the

cyanoenamine **29**, which is a versatile synthetic intermediate [20]. This method is very attractive because the conventional reactions require stoichiometric amounts of strong bases (Thorpe–Ziegler reaction).

An important feature of the present reaction is the chemoselective addition of activated nitriles to the CN triple bonds of nitriles in the presence of carbonyl groups, because of the strong coordination ability of nitriles toward metals. The iridium-catalyzed addition of ethyl cyanoacetate to 4-acetylbenzonitrile (**30**) gives ethyl (*Z*)-3-(4-acetylphenyl)-3-amino-2-cyano-2-propenoate (**31**, 59 %) chemoselectively, while the same reaction promoted by a conventional base such as AcONH₄ and NaOH gives ethyl 2-cyano-3-(4-cyanophenyl)-2-butenolate (**32**) (*E:Z* = 55:45) [20].



Scheme 7. Iridium-catalyzed Thorpe–Ziegler reaction.

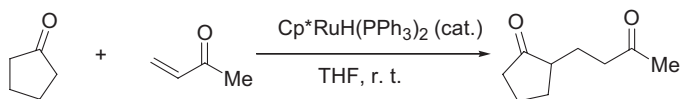
To activate simple alkanenitriles, more active iridium hydride catalysts, such as IrH₅(P-*i*-Pr₃)₂ are required. The IrH₅(P-*i*-Pr₃)₂-catalyzed cyclization of 1,5-dicyanopentane gives the corresponding cyanoenamine under neutral condition in 72 % yield [20]. This reaction can be rationalized by assuming a mechanism which involves C–H activation of nitrile.

1.1.1.7 The C–H Activation of Carbonyl Compounds

The catalyst RuH₂(PPh₃)₄ itself has no catalytic activity in the C–H activation of carbonyl compounds, and a more basic catalyst such as RuCpH(PPh₃)₂ and RuCp*H(PPh₃)₂ is required for activation of 1,3-dicarbonyl compounds. The catalytic Michael addition of 3-methyl-2,4-pentanedione to methyl vinyl ketone gave the corresponding adduct in 79 % yield [2].

The most important aspect is the α -C–H activation of simple ketones with a catalyst under neutral conditions. Typically, the C–H activation of cyclopentanone in the presence of methyl vinyl ketone and RuCp*H(PPh₃)₂ catalyst in THF at 60 °C gave 2-(3-oxobutyl)cyclopentanone (**33**) in 52 % yield [2, 21]. Michael addition of simple ketones is quite difficult because of undesirable side reactions such as polycondensation of ketones and polymerization of olefins. Therefore, synthons

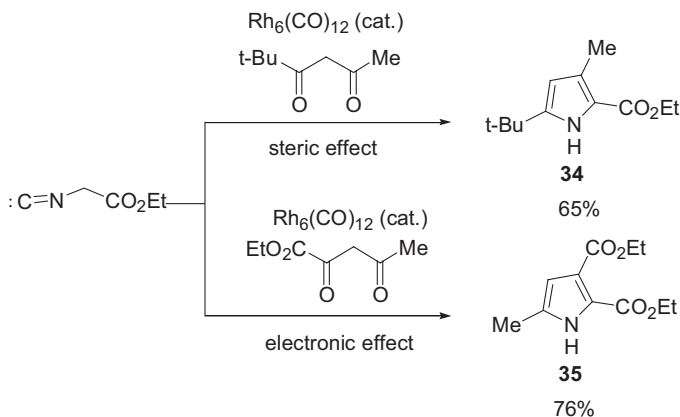
of ketones, such as enamines and silyl enol ethers, have been used. In this aspect, the present direct reaction has an advantage over the conventional methods in view of synthetic and environmental aspects.



Scheme 8. The C–H activation of ketones.

1.1.1.8 The C–H Activation of Isonitriles

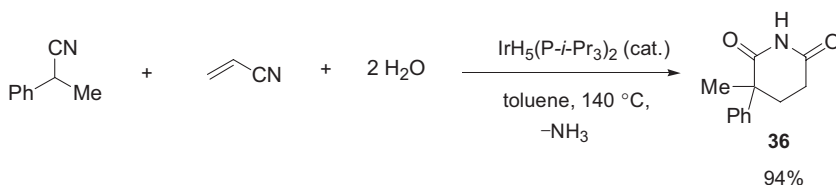
The concept of hetero atom effect for C–H activation led to the discovery of the rhodium and ruthenium-catalyzed C–H activation of isonitriles. Capture of the α -metalated intermediate thus formed by C–H activation with electrophiles such as carbonyl compounds provides a highly useful method for the formation of a carbon–carbon bond at the α -position of isonitriles under neutral conditions. Thus, ruthenium or rhodium-catalyzed addition of isonitriles to carbonyl compounds occurs to give the corresponding α,β -unsaturated formamides [22]. This reaction can be applied to rare methods for synthesis of pyrroles under catalytic reactions. Thus, using Rh₆(CO)₁₂ as catalyst the pyrrole derivatives **34** and **35** can be prepared regioselectively from 1,3-dicarbonyl compounds and isonitrile by controlling steric and electronic effects [22]. The mechanism of this reaction can be rationalized by assuming the α -C–H activation of isonitrile, insertion of carbonyl compound, reductive elimination to give the hydroxy compound, which undergoes dehydration to give the unsaturated formimide. In the reaction of 1,3-dicarbonyl compounds, the unsaturated formimide undergoes rhodium catalyzed decarbonylation to give the enamino intermediate which undergoes intramolecular cyclization to give pyrrole.



Scheme 9. The C–H activation of isonitriles.

1.1.1.9 Acid and Base Ambiphilic Catalysts for One-pot Synthesis of Glutalimides

In 1986, Murahashi et al. found that $\text{RuH}_2(\text{PPh}_3)_4$ **9** is the excellent catalyst which acts as Lewis acid under neutral conditions, and that hydration of nitriles [23, 24], amidation of nitriles with amines [23], and esterification of nitriles with alcohols [25] can be performed highly efficiently in the presence of catalyst **9**. Combination of the C–H activation of nitriles with the above Lewis acid-type reactions would provide new types of highly useful catalytic reaction. When one uses $\text{IrH}_5(\text{P-}i\text{-Pr}_3)_2$ as the ambiphilic catalyst that works as both Lewis acid and base, 2-phenylpropenenitrile, acrylonitrile, and water (1:1:2) occur to give the cyclocondensation product of 2-methyl-2-phenyl-glutarimide (**36**) in 84 % yield [26]. The reaction can be rationalized by assuming that the C–H activation of nitrile with iridium catalyst is followed by a Michael addition to acrylonitrile to give 1,3-dinitrile, which undergoes hydrolysis and intramolecular condensation reaction. These steps correspond to conventional multi-step processes which include base-promoted and acid-promoted reactions.

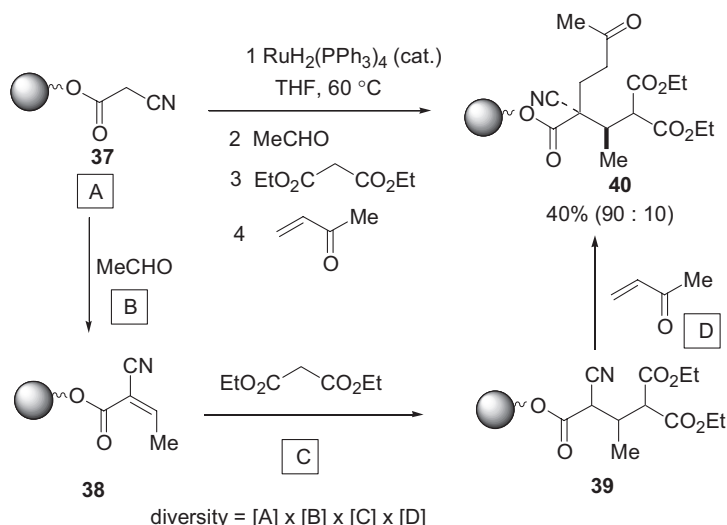


Scheme 10. Three-component reaction for the synthesis of glutalimides by the acid and base ambiphilic catalyst.

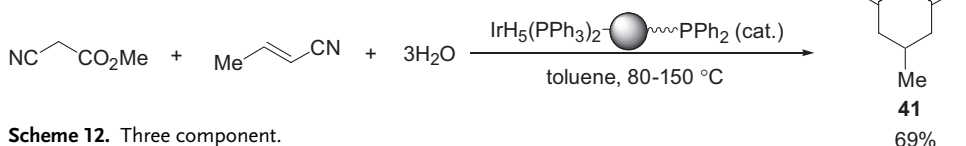
1.1.1.10 Application to Combinatorial Chemistry

Solid-phase synthesis is of importance in combinatorial chemistry. As already mentioned $\text{RuH}_2(\text{PPh}_3)_4$ catalyst can be used as an alternative to the conventional Lewis acid or base catalyst. When one uses polymer-supported cyanoacetate **37**, which can be readily obtained from the commercially available polystyrene Wang resin and cyanoacetic acid, the ruthenium-catalyzed Knoevenagel and Michael reactions can be performed successively [27]. The effectiveness of this reaction is demonstrated by the sequential four-component reaction on solid phase as shown in Scheme 11 [27]. The ruthenium-catalyzed condensation of **37** with propanal and subsequent addition of diethyl malonate and methyl vinyl ketone in THF at 50 °C gave the adduct **40** diastereoselectively in 40 % yield (*de* = 90:10).

Furthermore, using the polymer-supported acid–base ambiphilic catalyst of $\text{IrH}_5(\text{P-}i\text{-Pr}_3)_2$ the multi-step reaction using the conventional acid and base can be carried out as a one-pot reaction under neutral conditions. A series of glutalimides that are key compounds in medicine can be prepared readily [2] as shown in Scheme 12.



Scheme 11. Ruthenium-catalyzed four-component reaction and glutralimide synthesis by means of a polymer-supported iridium catalyst.



Experimental

(E)-Ethyl 2-cyano-3-(4-hydroxyphenyl)-2-propenoate (**10**) [8]

A mixture of ethyl cyanoacetate (0.113 g, 2.00 mmol), *p*-hydroxybenzaldehyde (0.249 g, 2.20 mmol), and $\text{RuH}_2(\text{PPh}_3)_4$ catalyst (0.06 mmol) in dry THF (0.5 mL) was stirred at room temperature for 24 h under argon. After removal of the solvent, the residue was purified by Kugelrohr distillation and chromatography on silica gel to give the product **10** in 98 % yield: m.p. 176.2–177.2 °C.

Ethyl 2-Cyano-4-formyl-2-methylbutanoate (**13**) [8]

A mixture of ethyl 2-cyanopropionate (2.0 mmol), acrylonitrile (2.2 mmol), and $\text{RuH}_2(\text{PPh}_3)_4$ (0.06 mmol) in dry THF was stirred at room temperature for 24 h under argon. Usual work-up and chromatography (SiO_2) gave the adduct **13** in 72 % yield.

3-[(*p*-Methoxycarbonylphenyl)amino]-2-cyano-2-methyl-3-(*p*-tolyl)propanenitrile (**18**) [8]

A mixture of 4-(methoxycarbonyl)-*N*-(4-methylbenzylidene)aniline (0.097 g, 0.39 mmol), 2-methylmalononitrile (0.048 g, 0.57 mmol), and $\text{RuH}_2(\text{PPh}_3)_4$ (0.026 g, 0.023 mmol) in dry THF (1.0 mL) was stirred under argon at room tem-

perature for 48 h. Usual work up and chromatography (SiO_2) gave the addition product (0.117 g, 91 %) as a colorless oil.

(Z)-3-Amino-4-methoxy-2-pivaloyl-2-butenenitrile (29) [20]

A mixture of methoxyacetonitrile (1.0 mmol), pivaloylacetonitrile (2.0 mmol), and $\text{IrH}(\text{CO})(\text{PPh}_3)_3$ (3 mol%) in dry THF (0.25 mL) was stirred at 120 °C for 12 h under argon in a sealed Pyrex tube. After removal of the solvent, the residue was purified by column chromatography (SiO_2) to give the corresponding cyanoenamine **29** in 96 % yield: m.p. 97.8 °C.

Synthesis of 2-methyl-4,5-dicarboethoxypyrrole (35) [22]

A mixture of ethyl acetylcyanoacetate (2.0 mmol), ethyl isocyanoacetate (1.0 mmol), and $\text{Rh}_4(\text{CO})_{12}$ (0.0075 mmol, 3 mol% based on Rh) in dry toluene (0.5 mL) was stirred under an argon atmosphere for 4 h at 80 °C. Usual work-up and chromatography (SiO_2) gave the corresponding pyrrole **35** in 76 % yield.

Synthesis of 2-methyl-2-phenylglutalimide (36) [26]

A mixture of phenylpropanenitrile (1.0 mmol), acrylonitrile (1.0 mmol), water (5.0 mmol), and $\text{IrH}_5(\text{PiPr}_3)_2$ catalyst (0.10 mmol) in THF (0.25 mL) was stirred in a sealed glass tube at 150 °C for 20 h under an argon atmosphere. After usual work up, the glutalimide product **36** was isolated by chromatographic separation on silica gel in 94 % yield.

1.1.2

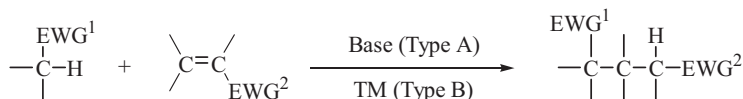
Palladium-Catalyzed Addition of Nitriles to C–C Multiple Bonds

Yoshinori Yamamoto and Gan B. Bajracharya

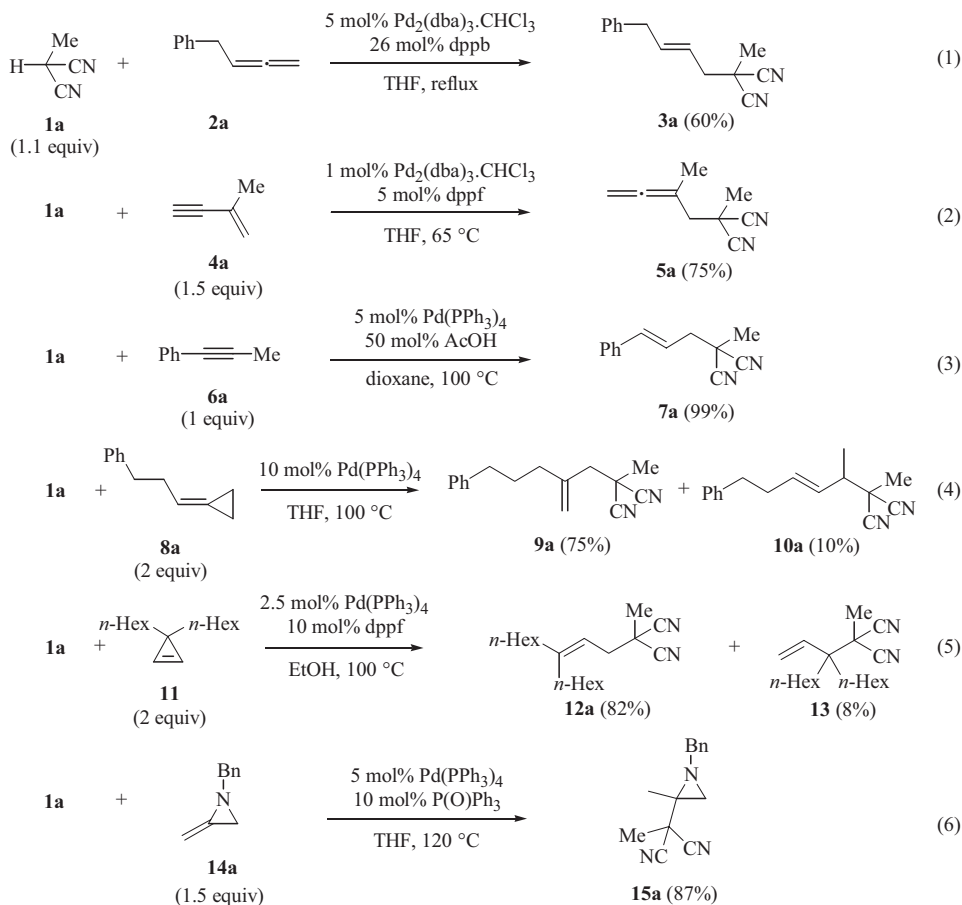
1.1.2.1 Introduction and Fundamental Examples

The formal addition of a C–H bond at activated methylenes and methynes (pronucleophiles) to activated alkenes in the presence of a base is well known as the Michael reaction (Scheme 1, Type A) [1]. In modern organic syntheses, the use of transition metal (TM) catalysts enables the C–H addition of activated methylenes and methynes to activated alkenes perfectly under neutral conditions (Scheme 1, Type B) [2]. In general, the nonfunctionalized carbon–carbon multiple bonds (for example, $\text{EWG}^2 = \text{H}$ in Scheme 1) are unreactive toward carbon nucleophiles because of their electron rich π -orbitals. The pioneering efforts by various research groups resulted in the development of transition metal-catalyzed addition of a C–H bond at active alkanes to such unactivated C–C multiple bonds. This reaction consists of the formal addition of a C–H bond across the C–C multiple bonds and is called a hydrocarbonation reaction. As a milestone in this hydrocarbonation area, early in the 1970s, Takahashi et al. reported the Pd-catalyzed addition of the C–H bond of pronucleophiles to 1,3-dienes [3]. The first Pd-catalyzed reaction of activated methylenes with unsubstituted allenes was apparently reported by Coulson [4]. The synthetic applications of this reaction were very limited. In the last decade, the Pd-catalyzed addition of C–H bonds to various unacti-

vated olefinic compounds has been developed as a powerful tool for the formation of C–C bonds [5]. As shown in Scheme 2, the hydrocarbonation of various unsaturated systems such as allenes **2** [6], enynes **4** [7], alkynes **6** [8], methylenecyclopropanes **8**[9] and cyclopropene **11**[10] proceeds very smoothly in the presence of palladium catalyst to give the corresponding olefinic derivatives. On the other hand,



Scheme 1. Formal C–H addition of activated methylenes and methynes to activated C–C multiple bonds.

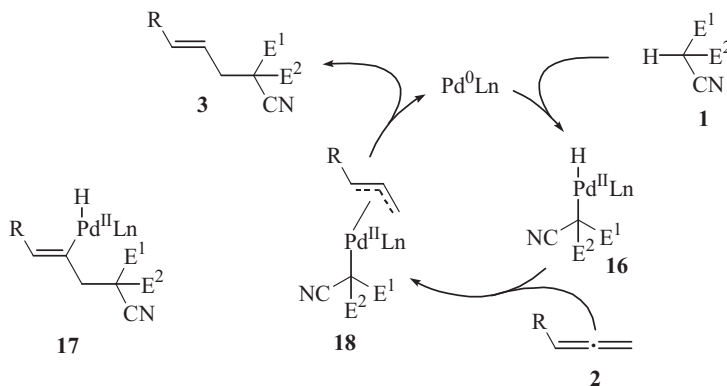


Scheme 2. Selected examples for Pd-catalyzed addition of nitriles to C–C multiple bonds; dba = dibenzylideneacetone; dppb = 1,4-bis(diphenylphosphino)butane; dppf = 1,1'-bis(diphenylphosphino)-ferrocene.

the hydrocarbonylation of methyleneaziridines **14** produces the non-ring-opened aziridines [11]. In many cases, the addition of small amounts of additives such as phosphine ligands or carboxylic acids is found to enhance the product yields and selectivity. The synthetic applications and mechanistic implications of the addition of a C–H bond at functionalized alkanes (especially nitriles as pronucleophiles) to C–C multiple bonds in Pd-catalyzed hydrocarbonylation reactions are highlighted herein. Examples of the activation of other kinds of pronucleophile in transition metal-catalyzed reactions are presented in Sect. IV.1.1.1 (transition metal-catalyzed activation of pronucleophiles).

1.1.2.2 Mechanism

A mechanistic rationale for the Pd-catalyzed addition of a C–H bond at nitriles to allenes is outlined in Scheme 3. The oxidative insertion of Pd(0) into the C–H bond of nitrile **1** produces the Pd(II) hydride species **16** (or alternatively a tautomeric structure $E^1E^2C=C=NPdHLn$ may be more suitable, where $E = H$, alkyl, aryl and/or EWG). Carbopalladation of the allene **2** would afford the alkenylpalladium complex **17** (carbopalladation mechanism), which would undergo reductive coupling to give the addition product **3** and regenerates Pd(0) species. As an alternative mechanism, it may be considered that the hydropalladation of allenes with the Pd(II) intermediate **16** gives the π -allylpalladium complex **18** which undergoes reductive coupling to afford the adduct **3** and a Pd(0) species (hydropalladation mechanism).

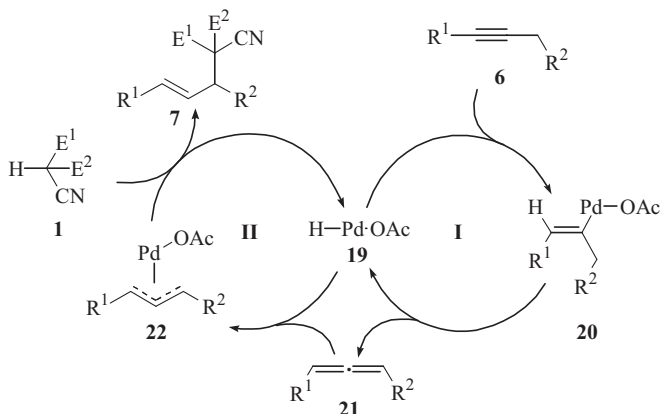


Scheme 3. C–H transformation to allenes: hydropalladation or carbopalladation mechanism.

Hydrocarbonylation of enyne proceeds via hydropalladation of enyne with **16**, which affords the exo methylene π -allylpalladium complex. Reductive elimination would lead to formation of **5**.

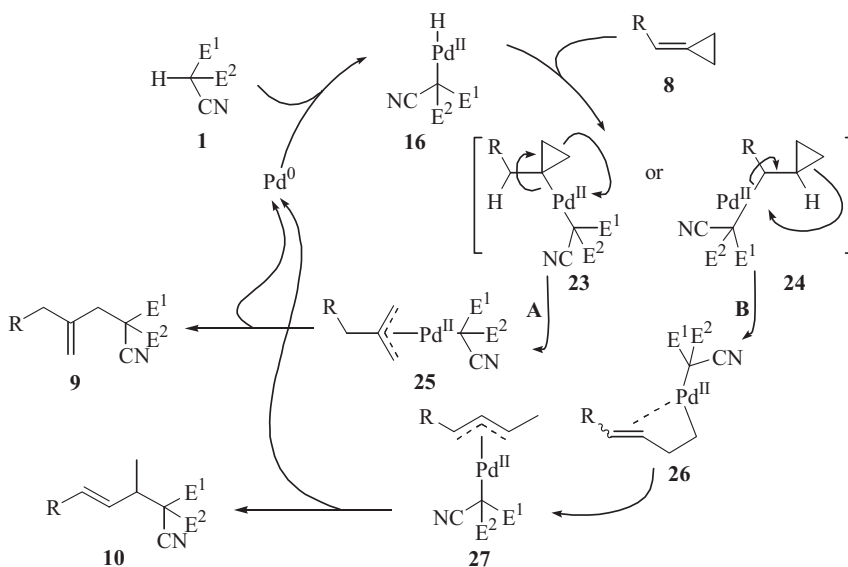
In the hydrocarbonylation of alkynes (Scheme 4), the hydropalladation-elimination of HPdOAc **19**, generated from Pd(0) and acetic acid, to internal alkynes **6** produces allenes **21** and the active catalyst (HPdOAc) (catalytic cycle I). The second hydropalla-

ation of allenes **21** with **19** would give the π -allylpalladium complexes **22**, which reacts with nitriles **1** to give the product **7** along with HPdOAc **19** (cycle II).



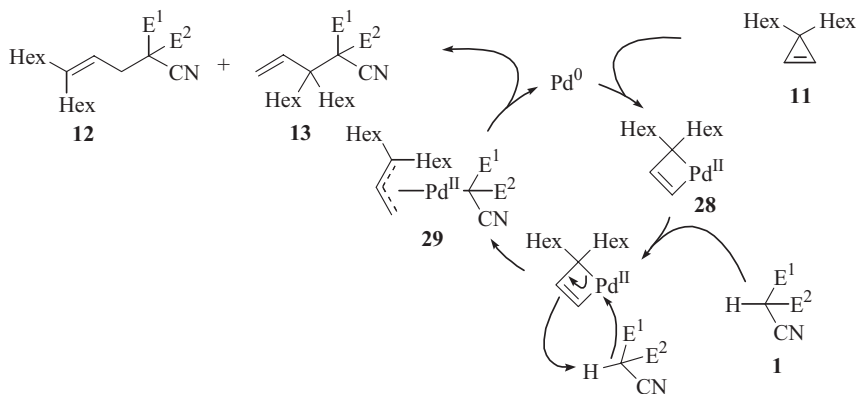
Scheme 4. C–H transformation to alkynes: hydropalladation mechanism.

In the hydrocarbonation of methylenecyclopropanes **8** with nitriles, the hydropalladation of **8** with **16** gives the alkylpalladium complexes **23** and/or **24** (Scheme 5). The complex **23** would undergo rearrangement by distal bond cleavage to give the π -allylpalladium **25** (route A). The reductive elimination of Pd(0) from **25** produces **9**. The palladium complex **24** would isomerize to the π -allylpalladium complex **27** via proximal bond cleaved ring-opened intermediate **26** (route B). The reductive elimination of Pd(0) from **27** gives **10**.



Scheme 5. C–H transformation to methylenecyclopropanes: hydropalladation mechanism.

The hydrocarbonylation of 3,3-dihexylcyclopropene proceeds via the formation of palladacyclobutene intermediate **28** (Scheme 6). The pallada-ene type reaction between **28** and **1** produces the π -allylpalladium intermediate **29**. Reductive elimination gives the allylated products **12** and/or **13**.



Scheme 6. C–H transformation to 3,3-dihexylcyclopropene: formation of palladacyclobutene.

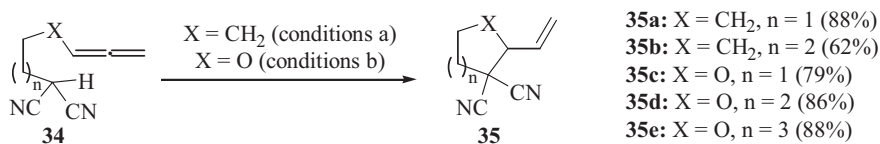
The Pd-catalyzed hydrocarbonylations of methyleneaziridines **14** do not proceed through the formation of a π -allylpalladium intermediates, instead via a chelation effect. The hydropalladation of methyleneaziridines with the $\text{Pd}(\text{II})$ hydride species **16**, followed by reductive elimination gives the non-ring-opened products **15**. It is noteworthy to mention that the palladium-catalyzed intermolecular or intramolecular addition of nitriles to carbon–carbon multiple bonds can be explained by the hydropalladation mechanism, except for the intramolecular addition to the $\text{C}\equiv\text{C}$ triple bond of alkynes (*vide infra*).

1.1.2.3 Scope and Limitations

C–H addition of cyano-based alkanes to the carbon–carbon double bond of allenes in the presence of palladium(0) affords the corresponding alkenes [6]. In most cases, addition of nitriles to allenes (especially monosubstituted allenes) selectively produces the γ -adducts with *E*-stereoselectivity (Scheme 2, Eq. 1) and with disubstituted allenes produces a mixture of *E* and *Z* isomers (Table 1, entry 1). With aryl allenes, the regioselectivity is controlled by the electronic effect of the substituents on the aromatic ring. As in substrate **2c**, the electron-withdrawing group substituted at the para position makes the β -carbon of the allene electrophilic and leads to predominant or exclusive formation of internal β -adducts (Table 1, entry 2). It was recently found that use of PhCO_2H as an additive dramatically enhances both rate and *E*-stereoselectivity in the addition of carbon pronucleophiles to allenes to give the corresponding γ -adducts (Table 1, entry 3). The Pd-catalyzed addition of nitriles to allenyl sulfides gives the γ -addition products with exclusive or predominant *E*-stereoselectivity (Table 1, entry 4). The double

addition product is obtained when the active methylenes (for example malono-nitrile **1b**) are used as reactant partners, because the mono adduct ($\text{PhSch}=\text{CHCH}_2\text{CH}(\text{CN})_2$) has a more reactive tertiary C–H bond (Table 1, entry 5). In marked contrast to the allenyl sulfides, the addition of alkoxy (or aryloxy) allenes to nitriles affords the α -addition products (Table 1, entry 6). The difference in this regioselectivity can be understood by the fact that (1) a sulfur substituent destabilizes a neighboring carbocation and stabilizes a neighboring carbanion, because of the electron-withdrawing effect of the sulfur atom, and (2) an oxygen substituent stabilizes a neighboring carbocation and destabilizes a neighboring carbanion, because of the electron-donating effect of the oxygen atom [12]. The Pd-catalyzed addition of nitriles with allenylstannanes proceeds smoothly affording the corresponding addition–substitution product (Table 1, entry 7). This reaction gives allylstannane intermediates as the first hydrocarbonation adducts; these react further with additional nitriles by transmetalation to give the double-alkylation products.


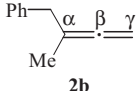
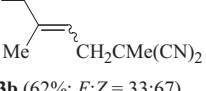
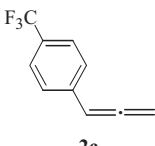
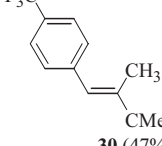
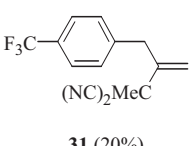
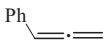
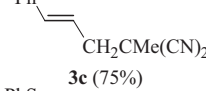
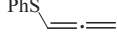
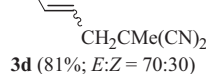

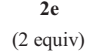
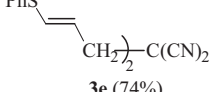
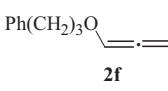
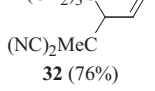
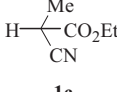
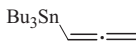
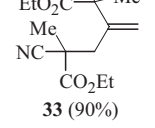
As an extension, carbocycles or heterocycles **35** are synthesized by intramolecular hydrocarbonation of alkyl- or alkoxyallenes **34** bearing active methyne groups at the terminus of the carbon chain, respectively (Scheme 7). With alkylallenes five-membered ring formation proceeds smoothly comparing to six-membered ring formation [6g]; this problem is not encountered with alkoxyallenes [6h].

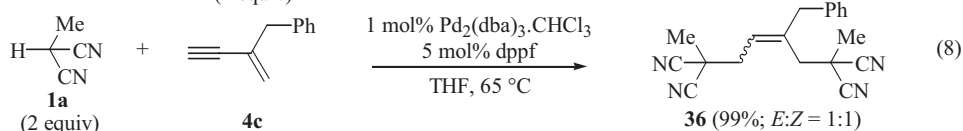
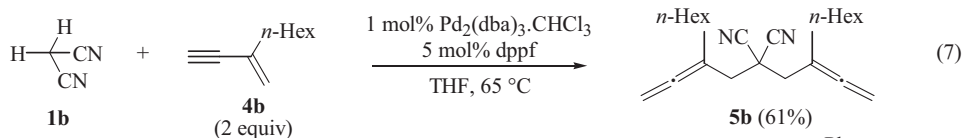


Scheme 7. Intramolecular C–H transformation to alkyl- and alkoxyallenes: (a) 5 mol% $[(\eta^3\text{-C}_3\text{H}_5)\text{PdCl}]_2$, 20 mol% dppf, THF, 70 °C under argon. (b) 1 mol% $\text{Pd}(\text{OAc})_2$, 2 mol% dppb, CH_2Cl_2 , rt under argon.

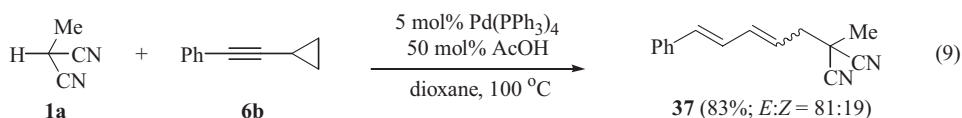
The addition of a C–H bond at nitriles to conjugated enynes is also feasible in the presence of Pd [7]. For example, methylmalononitrile **1a** reacts with 1.5 equiv. **4a** to give the corresponding allene **5a** via 1,4-addition regioselectively (Scheme 2, Eq. 2) [7a]. The nucleophilic portion is selectively added to the terminal olefinic carbon of the enyne rather than the triple bond. The active methylene in the presence of two equivalents of enynes undergoes double addition as expected and gives 1,3-diallenylalkanes (Eq. 7) [7b]. When excess nitrile is used, further addition of nitrile to the initially generated allenyl double bond occurs to give the 1,3-bis adduct (Eq. 8). It should be pointed out that the scope of this reaction is limited by the structure of the enyne. Addition of nitriles to the enynes, substituted at the alkyne moiety is very sluggish and addition to enynes substituted at the terminal olefinic position, does not proceed.

Table 1. Selected examples for addition of nitriles to allenes^a.

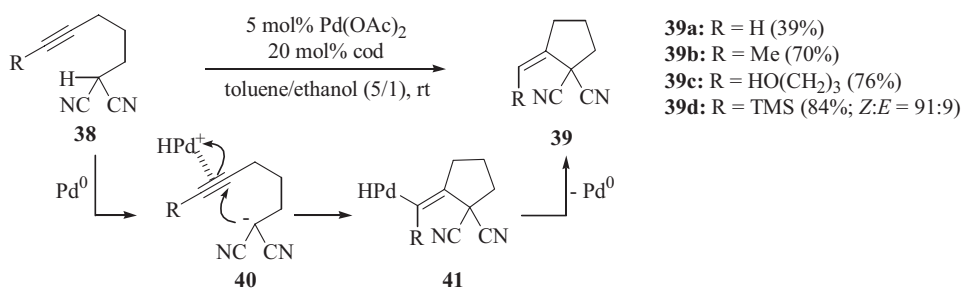
Entry	Nitrile 1	Allene 2	Products	Ref.
1	 1a	 2b	 3b (62%; <i>E:Z</i> = 33:67)	6a
2	1a	 2c	 30 (47%) +  31 (20%)	6b
3 ^b	1a	 2d	 3c (75%)	6c
4	1a	 2e	 3d (81%; <i>E:Z</i> = 70:30)	6d
5	 1b	 2e (2 equiv)	 3e (74%)	6d
6	1a	 2f	 32 (76%)	6e
7 ^c	 1c (2.2 equiv)	 2g	 33 (90%)	6f

^a 5 mol% Pd₂(dba)₃·CHCl₃, 26 mol% dppb, THF, reflux under argon.^b 5 mol% Pd(PPh₃)₄, 10 mol% PhCO₂H, dioxane, 100 °C under argon.^c 10 mol% Pd₂(dba)₃·CHCl₃, 52 mol% dppb, THF, reflux under argon.

The Pd-catalyzed allylation of carbon nucleophiles using allylic substrates, such as allylic acetates, halides, pseudohalides, and carbonates, under basic conditions is a well-recognized reaction in modern organic chemistry (Tsuji–Trost reaction) [13]. This procedure requires a stoichiometric amount of base to generate the nucleophile. The reaction of some alkynes with nitriles in the presence of the $\text{Pd}(\text{PPh}_3)_4$ –AcOH catalytic system provides an alternative method for the allylation [8a, b]. The reactions usually proceed regioselectively. For example, methylmalononitrile **1a** on treating with **6a** affords the adduct **7a** as a sole product (Scheme 2, Eq. 3). Interestingly, the reaction of cyclopropyl phenyl acetylene **6b** produces the linear adduct **37** (Eq. 9).



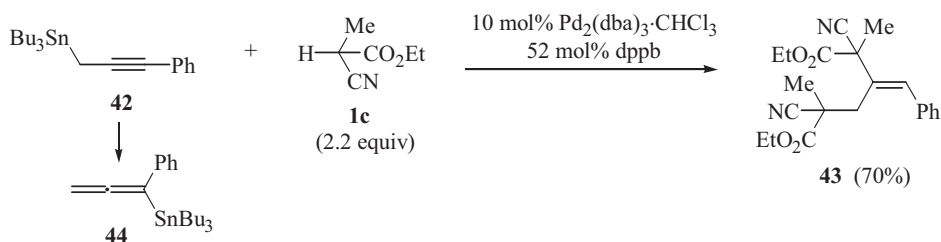
The intramolecular C–H transformation at ϵ -alkynyl malononitriles **38** proceeds using $\text{Pd}(\text{OAc})_2$ –cod (cod = cycloocta-1,5-diene) (or oct-1-ene) catalytic system to give the *Z* isomer of the corresponding carbocycles **39** (Scheme 8) [8c]. The formation of the *Z* isomer suggests the reaction does not proceed through a π -allylpalladium intermediate; the *E* isomer must be produced predominantly if it is involved as a reaction intermediate. Probably, the reaction pathway first involves the formation of cationic hydride complex (HPd^+) by abstraction of a proton from $\text{HC}(\text{CN})_2\text{R}$ by $\text{Pd}(0)$. Coordination of HPd^+ to the triple bond and subsequent trans-carbopalladation affords the vinyl palladium species **41**. The reductive elimination of $\text{Pd}(0)$ leads to the cyclization product **39**. This type of reaction for a substrate which bears a terminal alkyne unit ($\text{R} = \text{H}$) is sluggish; this may be because of the oxidative addition of $\text{Pd}(0)$ into the C–H bond of the terminal alkyne. The scope of this reaction is limited with the substrate bearing two cyano groups at the terminus.



Scheme 8. Intramolecular C–H transformation to alkynes: cationic mechanism.

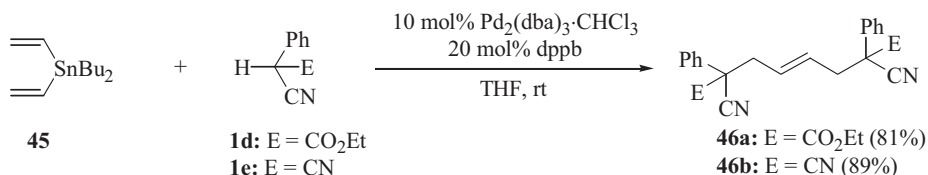
It has already been mentioned that allenylstannanes undergo addition–substitution reactions with nitriles (Table 1, entry 7). Prop-2-ynylstannane derivatives also have similar reactivity with nitriles and give addition-substitution products [6f]. As an example, 3-phenylprop-2-ynyl(tributyl)stannane **42** reacts with ethyl-2-

cyanopropionate **1c** to produce **43** (Scheme 9). Interestingly, treatment of **42** in the presence of catalytic amounts of $\text{Pd}_2\text{dba}_3 \cdot \text{CHCl}_3$ gives the isomerized allenylstannane **44** in essentially quantitative yield. Therefore, obviously the reaction of **42** would proceed through the allenylstannane **44**.



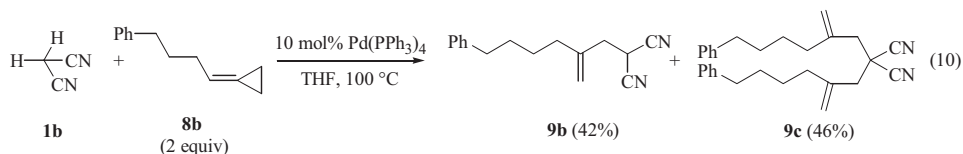
Scheme 9. C–H transformation to alkynylstannanes via formation of allenylstannanes.

The vinyltin **45** also can be used as an unsaturated system for C–H transformation of nitriles **1d** and **1e** producing the corresponding alkylative dimerization products of the vinyl group, 1,4-disubstituted butene derivatives **46** (Scheme 10) [14]. The reaction proceeds in a stereoselective fashion to give the trans isomer selectively. Malononitrile does not react with the vinyltin under the reaction conditions.

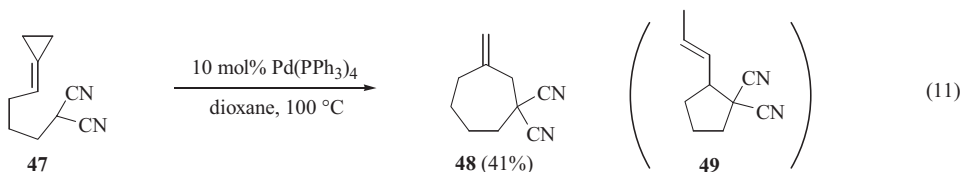


Scheme 10. C–H transformation to vinyltins.

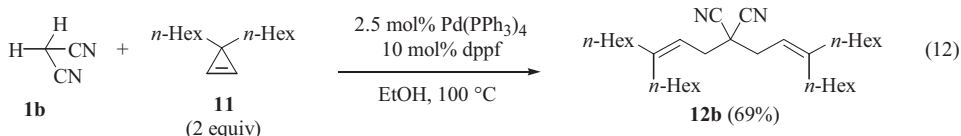
Pd-catalyzed C–H transformation at nitriles to methylenecyclopropanes **8** affords the terminal **9** and internal alkenes **10**, either exclusively or as a mixture of both (Scheme 2, Eq. 4) [9]. The selectivity of product formation depends on the mode of hydopalladation of the carbon–carbon double bond of the methylenecyclopropane and ring opening. Ring opening normally occurs at the distal bond. Also, the mode of ring opening of methylenecyclopropane depends on the chain length of the substituent at the exomethylene carbon. In the addition of malononitrile **1b** to **8b**, both monoalkylation and dialkylation products are obtained as a 1:1 mixture (Eq. 10).



Analogously, ω -cyclopropylidenealkylmalononitrile **47** is converted under the intramolecular C–H transformation to produce the 7-membered carbocycle **48**. Other possible products such as the 5-membered carbocycle **49** are not produced under the reaction conditions (Eq. 11) [9b, c].



The addition of nitriles to 3,3-dihexylcyclopropene **11** produces the corresponding allylated nitriles (Scheme 2, Eq. 5) [10]. The diallylation product **12b** is isolated in the reaction with the active methylene **1b** (Eq. 12). The non-ring-opened products **15** are produced in the Pd-catalyzed hydrocarbonation of methyleneaziridines **14** (Scheme 2, Eq. 6) [11]. Although this reaction can proceed in the presence of Pd catalyst only, the use of phosphine monodentate ligands provides better results.



Palladium catalysts have great value in the addition of a C–H bond at alkanes (activated with at least one cyano group and/or other electron withdrawing groups such as COMe, CO_2Et , SO_2Ph etc.) to unactivated C–C multiple bonds. Parallel to the hydrocarbonation reaction, addition of hydrogen–heteroatom bonds (for example H–N bonds and H–O bonds) across C–C multiple bonds is another most important and intriguing subjects in organic chemistry [5, 9c, 15]. Furthermore, the intramolecular version of these reactions provides one of the best and most straightforward ways to obtain nitrogen- and oxygen-containing heterocycles.

Several catalytic systems have been investigated for hydroamination of unsaturated bonds [16]. Takahashi et al. reported the telomerization of 1,3-dienes in the presence of an amine leading to octadienylamine or allylic amines when palladium catalysts are used in association with monodentate or bidentate phosphine ligands, respectively [17]. Dieck et al. demonstrated the beneficial effect of addition of an amine hydroiodic salt in the hydroamination reaction of 1,3-dienes in which the allylic amines are produced via an intermediate π -allyl palladium complex [18]. Coulson reported the Pd-catalyzed addition of amines to allenes where dimerization is incorporated [4]. This reaction presumably proceeds via a cyclic palladium intermediate in which the Pd activates the olefinic bond for nucleophilic attack; the reactions are therefore different from pronucleophilic additions.

Cazes et al. reported the Pd-catalyzed intermolecular hydroamination of substituted allenes using aliphatic amines in the presence of triethylammonium iodide leading to allylic amines [19]. In a way similar to the Pd-catalyzed hydrocarbonylation reactions we reported that the hydroamination of allenes [20], enynes [21], methylenecyclopropanes [22], and cyclopropene [10] proceeds most probably via oxidative addition of an N–H bond under neutral or acidic conditions to give allylic amines. The presence of benzoic acid as an additive promotes the Pd-mediated inter- and intramolecular hydroamination of internal alkynes [23]. Intramolecular hydroamination has attracted more attention in recent years, because of its importance in the synthesis of a variety of nitrogen-containing heterocycles found in many biologically important compounds. The metal-catalyzed intramolecular hydroamination/cyclization of aminoalkenes, aminodienes, aminoallenes, and aminoalkynes has been abundantly documented [23].

The transition metal-catalyzed addition of alcohols to unsaturated systems has not been widely investigated. Reports on addition of alcohols to 1,3-diene [24] or allene [25] have appeared but have very limited scope. We recently reported the palladium/benzoic acid-catalyzed inter- and intramolecular addition of alcohols to alkynes in which various acyclic and cyclic allylic ethers are produced [26]. The Pd-catalyzed addition of alcohols to alkylidenecyclopropanes proceeds smoothly providing a powerful tool for synthesis of allylic ethers [27a]. An intramolecular version of the hydroalkoxylation has been demonstrated in which the phenol-tethered alkylidenecyclopropanes undergo facile cyclization to give exomethylene products [27b].

Several reports on transition metal-catalyzed hydrocarboxylation for the preparation of carboxylic esters have appeared which involve the nucleophilic addition of carboxyl groups to metal-coordinated C–C multiple bonds of 1,3-dienes [28], enynes [29], and alkynes [30]. In contrast, we observed the activation of carboxylic acids in Pd-catalyzed hydrocarboxylation of aromatic allenes, which produces allyl esters in excellent yield with high γ -selectivity [31]. This reaction involves the activation of carboxylic acid-forming H–Pd–OCOR and proceeds through insertion of the double bond into the H–Pd bond. Trost et al. reported the Pd-catalyzed hydrocarboxylation of in-situ-generated allenes from propargyl derivatives [32]. Remarkably, the intramolecular version of this reaction proceeds efficiently to give macrocycles. The Pd-catalyzed hydrocarboxylation of methyleneaziridines provides a highly useful method for constructing α -amidoketones [33].

Experimental

2-Cyano-2-methyl-6-phenyl-4(E)-hexenenitrile (3a)

A mixture of 65 mg (0.5 mmol) 4-phenyl-1,2-butadiene (**2a**), 44 mg (0.55 mmol) methylmalononitrile (**1a**), 26 mg (0.025 mmol, 5 mol%) $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$, 54 mg (0.13 mmol, 26 mol%) dppb, and 3 mL dry THF was heated under reflux under an argon atmosphere (a round-bottomed flask or pressure vial can be used as reaction vessel). The reaction course was monitored by TLC and/or GC analysis. After completion of the reaction the mixture was filtered through a short alumina col-

umn with THF as eluent and then concentrated. The product was isolated by column chromatography: 63 mg (60%) of **3a**. ^1H NMR (CDCl_3 , 270 MHz): δ = 1.75 (s, 3H), 2.62 (dd, J = 7.0, 1.0 Hz, 2H), 3.45 (d, J = 7.0 Hz, 2H), 5.60 (dt, J = 14.0, 7.0, 1.0 Hz, 1H), 5.95 (dt, J = 14.0, 7.0, 1.0 Hz, 1H), 7.25 (m, 5H). Anal. Calcd for $\text{C}_{14}\text{H}_{14}\text{N}_2$ (210.2744): C, 79.967; H, 6.710; N, 13.332. Found: C, 79.746; H, 6.847; N, 13.178.

1.1.3

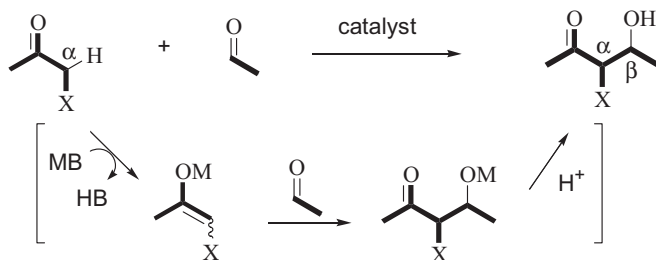
Asymmetric Catalytic C–C Coupling in the Position α to Carbonyl Groups

1.1.3.1 Direct Catalytic Aldol Reactions

Claudio Nicolau and Mikel Oiarbide

1.1.3.1.1 Introduction and Fundamental Examples

The direct catalytic aldol addition reaction involves the skeletal and functional transformation depicted in Scheme 1. Accordingly, a carbonyl compound bearing at least one α H atom reacts with (most often) an aldehyde to produce a β -hydroxy carbonyl, or aldol, adduct under the action of a catalyst. This direct transformation should be distinguished from the sequential process which involves the irreversible generation of a metal enolate or equivalent in a separate step and the final protonation step (path in brackets). For the sequential process, the method is well developed using several metal enolates, particularly boron enolates [1], and silyl enolates and silyl ketene acetals (Mukaiyama reaction) [2]. In general, for any aldehyde other than formaldehyde used as electrophile, a new stereocenter at the β position of the aldol is formed, and the α position may also be stereogenic when the starting carbonyl pronucleophile bears additional substituents at α ($X \neq \text{H}$). Thus this reaction enable entry to stereochemically diverse aldol substructures which are widespread in natural products. Not surprisingly, control of the stereochemistry during aldol additions is of central importance [3, 4]. Nature has solved this problem at the biosynthetic level by using enzymes as catalysts: class I and class II aldolases are known to catalyze the aldol addition reaction as a fundamental C–C bond-forming step en route to sugars [4, 5]. Also catalytic antibodies capable of promoting direct aldol addition reactions have been identified [6].



Scheme 1. The direct, catalytic aldol addition reaction compared with the sequential aldol addition process (general pictogram).

Apart from enzymes and catalytic antibodies, chemical catalysis has been shown to be of utility for such a transformation by using either metal-containing complexes or purely organic molecules. In both cases, the catalyst plays a key role in activating both the pronucleophilic carbonyl compound and the electrophilic aldehyde; it also imparts effective stereoselection. The most representative metal–ligand complexes and organocatalysts yet reported in this context [7] are depicted in Figs. 1 and 2, respectively.

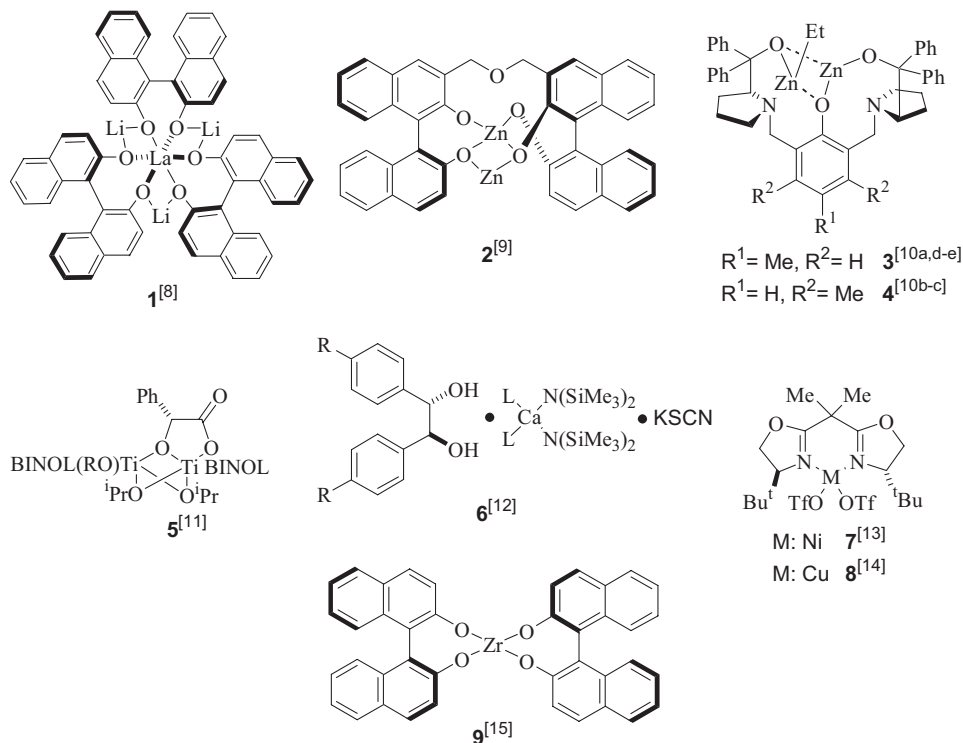


Figure 1. Some outstanding metal–ligand complexes of utility in the direct catalytic asymmetric aldol addition reaction.

An example that illustrates the potential of this catalytic C–C bond-forming process to build up key structural subunits of natural products is shown in Scheme 2. The reaction of acetophenone with aldehyde **18** in the presence of 8 mol% catalyst **1** affords the aldol adduct **19** in 70% yield and 93% ee, which is subsequently transformed into **20**, a key intermediate of the anticancer agent epothilone A [8b]. Similarly, Scheme 3, the aldol reaction of hydroxyacetylfuran **21** with valeraldehyde in the presence of 5 mol% catalyst **3** produces syn diol **23** with high efficiency [10d]. Further chemical elaboration of **23** leads to **24**, a key intermediate in the synthesis of (+)-boronolide, a folk medicine with emetic and anti-malaria activity.

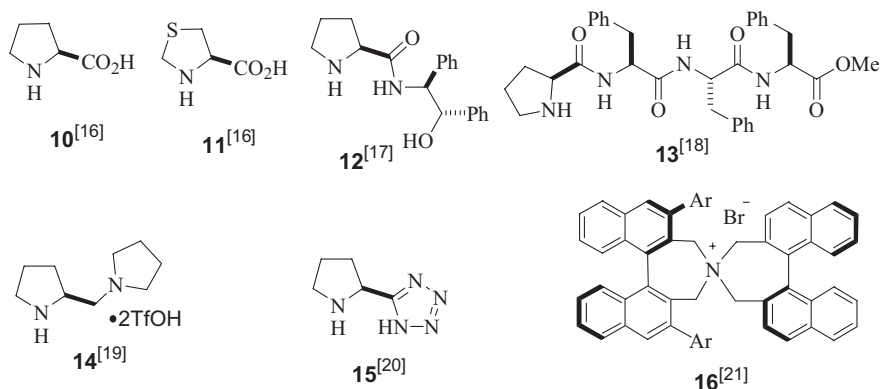
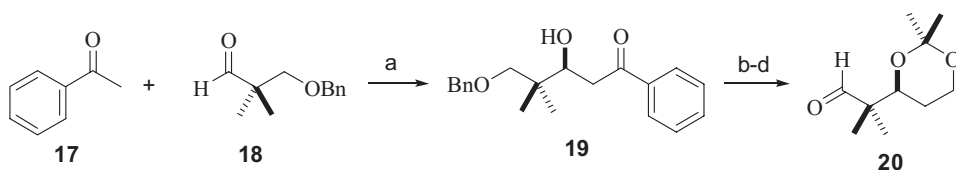
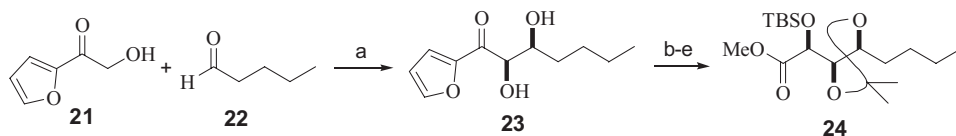


Figure 2. Purely organic molecules of utility in the direct catalytic asymmetric aldol addition reaction.



Scheme 2. Synthesis of the key intermediate en route to epothilone A based on a catalytic, asymmetric direct aldol addition of acetophenone (5.7 mmol scale) and an α -branched acyclic aldehyde. (a) **1** (8 mol%), KHMDS

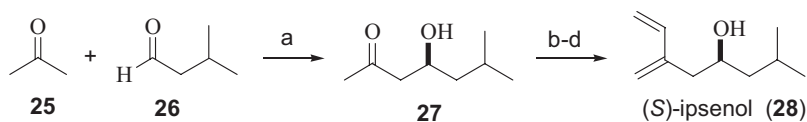
(7.2 mol%), H_2O (16 mol%), THF, -20°C , 24 h, 70 % (93 % ee). (b) LiAlH_4 . (c) $(\text{CH}_3\text{O})_2\text{C}(\text{CH}_3)_2$. (d) Li , NH_3 , $t\text{-BuOH}$, $(\text{COCl})_2$, DMSO, Et_3N , 93 % (three steps) [8b].



Scheme 3. Synthesis of the key intermediate en route to (+)-boronolide based on a catalytic, asymmetric direct aldol addition reaction of 2-hydroxyacetyl furan and valeraldehyde. (a) **3** (5 mol%), MS 4 Å, THF, -35°C , 12 h, 78 % (of isolated syn product, 97 % ee).

(b) DMP, Amberlyst 15, CH_2Cl_2 , rt, 98 %. (c) L-Selectride, THF, -100°C ; H_2O_2 , NaOH, 89 %. (d) *tert*-Butyldimethylsilyl trifluoromethanesulfonate (TBSOTf), 2,6-lutidine, CH_2Cl_2 , 0°C , 98 %. (e) RuCl_3 (cat.), NaIO_4 , CCl_4 , CH_3CN , H_2O ; CH_2N_2 , Et_2O , 70 % [10d].

Proline-catalyzed direct aldol reactions have also been employed in the context of natural products synthesis, as is illustrated in the synthesis of the bark beetle pheromone (*S*)-ipsenol of Scheme 4 [16d].

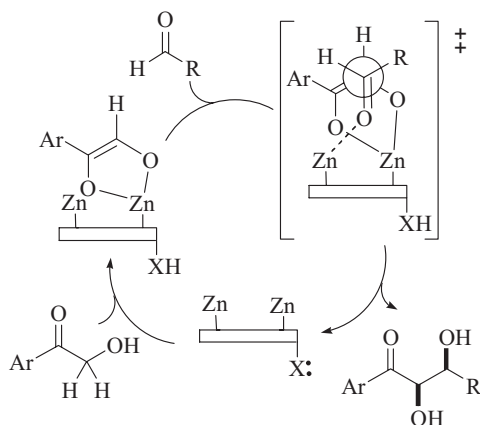


Scheme 4. Synthesis of (S)-iposenol using the proline-catalyzed direct aldol addition reaction as key transformation. (a) L-Proline (10–20 mol%), acetone (solvent), 3–7 days, 34 % (73 % ee). (b) TBSCl, imidazole;

KHMDS, *N*-(5-chloro-2-pyridyl)bis(trifluoromethanesulfonimide). (c) Vinyl tributylstannane, $\text{Pd}(\text{PPh}_3)_4$ (cat.), LiCl, THF, 95 %. (d) *tert*-Butyldimethylsilyl fluoride (TBAF), THF, 90 %.

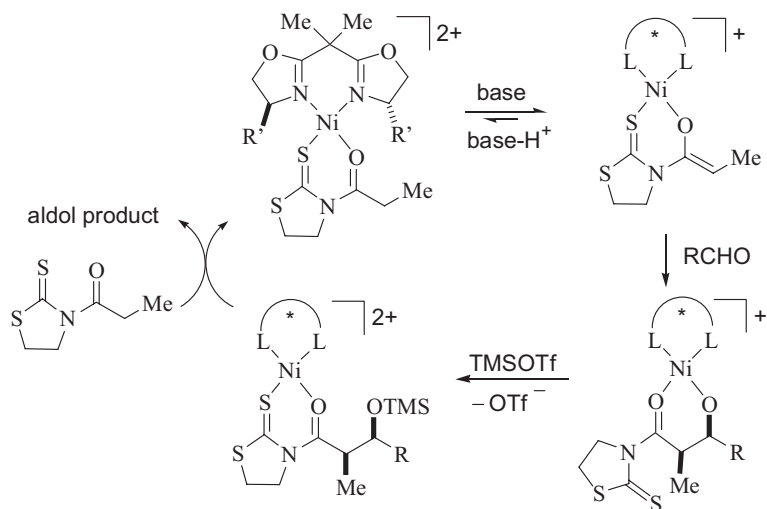
1.1.3.1.2 Mechanism

The mechanisms for metal-catalyzed and organocatalyzed direct aldol addition reactions differ one from another, and resemble the mode of action of the type II and type I aldolases, respectively. Some metal–ligand complexes, for example, **1–4** and **9** are considered to have a bifunctional character [22], embodying within the same molecular frame a Lewis acidic site and a Brønsted basic site. Whereas base would be required to form the transient enolate species as an active form of the carbonyl donor, the Lewis acid site would coordinate the acceptor aldehyde carbonyl, increasing its electrophilicity. By this means, both transition state stabilization and substrates preorganization would be provided (see Scheme 5 for a proposal).



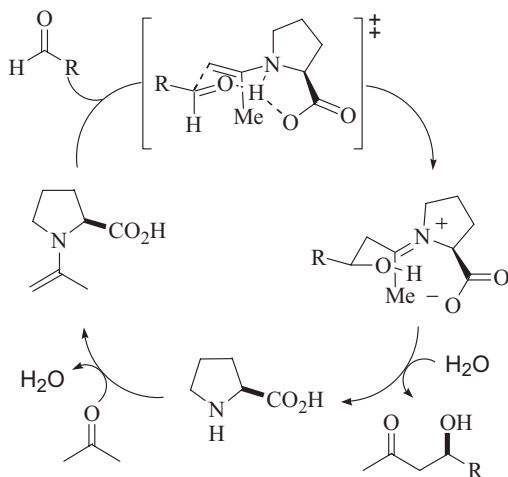
Scheme 5. Proposed mechanistic pathway of the Zn-catalyzed direct aldol addition reaction of hydroxyacetophenone [9, 10c].

In some instances, for example the reactions involving complexes **7** and **8**, the metal–chiral ligand complex alone does not suffice for good performance and addition of external base in either catalytic or (over)stoichiometric quantity, or even trimethylsilyl triflate, is required [13, 14]. Apparently, in Scheme 6, although the metal center(s) is (are) fundamental for a well-ordered transition state and for acceptor activation, the external base is required for deprotonation leading to formation of a transient metal enolate.



Scheme 6. Proposed catalytic cycle for the direct asymmetric aldol addition reaction of *N*-propionylthiazolidinethione [13].

For the proline- and proline congener-catalyzed aldol reaction [23, 24], a mechanism based on enamine formation is proposed [25], Scheme 7. The catalytic process starts with condensation of the secondary amino group of proline with a carbonyl substrate leading to a nucleophilic enamine intermediate, which mimics the condensation of the active-site lysine residue with a carbonyl substrate in type I aldolases. The adjacent carboxylic acid group of the enamine intermediate



Scheme 7. Proposed enamine mechanism of the proline-catalyzed direct aldol addition reaction of acetone [25].

then directs the approach of the electrophile by formation of a specific hydrogen bond in the transition-state structure. When the addition step occurs, iminium ion is hydrolyzed to release the product aldol and regenerates the catalyst (L-proline).

1.1.3.1.3 Scope and Limitations

For satisfactory chemo- and stereoselectivity, most catalytic, direct cross-aldol methods are limited to the use of non enolizable (aromatic, α -*tert*-alkyl) or kinetically non enolizable (highly branched, α,β -unsaturated) aldehydes as acceptor carbonyls. With aromatic aldehydes, however, enantioselectivity is sometimes moderate, and the dehydration side-product may be important. With regard to the donor counterpart, the best suited pronucleophile substrates for these reactions are symmetric ketones (acetone) and ketones with only one site amenable for enolization (acetophenones). With symmetric cyclic or acyclic ketones superior to acetone, syn/anti mixtures of variable composition are obtained [8b, 11, 19a]. Of particularly broad scope is the reaction of *N*-propionylthiazolidinethiones with aldehydes, which regularly gives high enantioselectivity of the syn aldol adduct of aromatic, α,β -unsaturated, branched, and unbranched aldehydes [13].

Donor carbonyl compounds bearing α -hetero substituents have also been applied satisfactorily. Of remarkable performance and synthetic relevance is the use of hydroxyacetone and other α -hydroxy ketones such as hydroxyacetophenones. High syn and enantioselectivity are often achieved in reactions with α -hydroxy ketones leading to the corresponding α,β -dihydroxy carbonyls by using either organometallic catalysis [9, 10c] or organocatalysis [16b, c]. Remarkably, when peptide **13** is used as catalyst, reversal of the aldol chemoselectivity with hydroxyacetone is observed, leading to the unusual 1,4-diol adduct [18]. α -Amino carbonyl surrogates are also suitable substrates. For example, both α -diazo esters, under organometallic catalysis [15], and glycine Schiff bases, under chiral ammonium salt catalysis [21], render the corresponding α -amino aldol adducts. Although not general, pyruvate esters can also act as carbonyl acceptors, efficiently leading to the self condensation aldol product [14].

The enantioselective aldol coupling of non-equivalent aldehydes [26] has been an elusive task until very recently. Now the task is affordable in both intermolecular [27] and intramolecular [28] reactions using proline as the only catalyst. From the former strategy, β -hydroxyaldehydes with stereogenic quaternary carbon centers [19b] or key acyclic intermediates of sugar synthesis mimicking enzymes can be accessed [29], while from the latter straightforward entry into enantiomerically pure cyclohexanols is provided through an enol-exo cyclization. An alternative method for catalytically generating transient metal enolates and submitting them to an aldol reaction is the treatment of enones or alkyl enoates with hydrosilane or molecular hydrogen as the stoichiometric reducing agent in the presence of iridium and rhodium catalysts. Under these conditions both intramolecular [30] and intermolecular [31] direct, catalytic enantioselective reductive aldol reactions have been achieved to afford the corresponding acyclic and cyclic aldol products.

Table 1. Examples of the structural diversity and functional versatility of this C–C bond-forming process.

Donor carbonyl	Aldehyde R^2 CHO	Product	Yield (%)	syn/anti	ee (%)	Ref.
	R^2 : t Bu		75	--	88	8b
	R^2 : PhCH ₂ C(Me) ₂		85	--	89	8b
	R^2 : i Pr		62	--	98	10a
	R^2 : Ph		78	--	83	10b
	R^2 : 4-NO ₂ -Ph		89	--	91	10b
	R^2 : i Pr		97	--	96	16a
	R^2 : t Bu		51	--	>99	17
	R^2 : c C ₆ H ₁₁		77	--	98	17
	R^2 : CH ₂ =CHCH ₂ C(OEt) ₂		76	--	>98	10e
	Ar: Ph R^2 : i Pr		89	93:7	93	10c
	Ar: furyl R^2 : c C ₆ H ₁₁		90	86:14	96	10c
	Ar: 2-MeOPh R^2 : i Pr		83	97:3	98	9b-c
	Ar: 2-MeOPh R^2 : BnOCH ₂		84	72:28	96	9b-c
	R^2 : i Pr		62	<5:>95	>99	16b-c
	R^2 : Ph(Me)CH		51	<5:>95	>95	16b-c
	R^2 : Ph		81	94:6	97	13a
	R^2 : MeCH=CH		46	93:7	97	13a
	R^2 : n Et		84	97:3	90	13a
	R^2 : Ph		65	–	87	15
	R^2 : PhCH=CH		72	–	79	15
	R^2 : PhCH ₂ CH ₂		77	23:77	91	21
	R^2 : CH ₂ =CHCH ₂ CH ₂		71	29:71	90	21
	R^2 : c C ₆ H ₁₁		78	45:55	93	21
	R^2 : Et		80	20:80	99	27
	R^2 : Ph		81	25:75	99	27
	R^2 : i Pr		80	4:96	98	27
	R^2 : Ph		32	--	96	19b
	R^2 : p -NO ₂ Ph		94	--	95	19b
	R^2 : Et		78	72:28	74	11
	R^2 : Ph		85	91:9	91	11
	R^1 : Bn R^1 : TIPS		73	20:80	98	29a
			92	20:80	95	29a
			92	67:33 (d.r.)	9	28
			95	91:9 (d.r.)	99	28

Experimental

Aldol Reaction of 2-Hydroxyacetylfuran with Cyclohexanecarboxaldehyde Catalyzed by **3** [**10a**, **c**]

Chiral ligand synthesis [**10a**]

To a solution of L-proline methyl ester hydrochloride (6.36 g, 38.4 mmol) and triethylamine (10.2 mL, 80 mmol) in CH_2Cl_2 (60 mL) was added a solution of 2,6-bis(bromomethyl)-*p*-cresol (4.7 g, 16 mmol) in CH_2Cl_2 (20 mL) at room temperature and the mixture was stirred at same temperature for 24 h. The mixture was concentrated to half volume under vacuum and the residue purified by silica gel column chromatography (PE–EtOAc 1:1). To a solution of this residue (6.8 g, 17.4 mmol) in THF (60 mL) was added a solution of phenylmagnesium chloride (2 M in THF, 78 mL, 156.6 mmol) at room temperature and the mixture was stirred at the same temperature for one day. Sat. NH_4Cl was added to the reaction mixture and the mixture was extracted with ether. The organic layer was washed with brine and dried over magnesium sulfate. Evaporation of the solvent under the reduced pressure and purification of the residue by silica gel column chromatography (PE–EtOAc 9:1–4:1) afforded the chiral ligand required.

Catalyst generation

Under an argon atmosphere, a solution of diethylzinc (1.0 M in hexane, 0.2 mL, 0.2 mmol) was added to the solution of the amino alcohol ligand prepared as above (64 mg, 0.1 mmol) in THF (1 mL) at room temperature. After stirring for 30 min at the same temperature with evolution of ethane gas the resulting solution was used as a ca 0.09 M solution of **3**.

Aldol reaction [**10c**]

Under an argon atmosphere, a solution of the zinc catalyst **3** (0.1 M in THF, 0.25 mL, 0.025 mmol) was added to a suspension of powdered molecular sieves 4 Å (100 mg, dried at 150 °C under vacuum overnight), cyclohexanecarboxaldehyde (56 mg, 61 μL , 0.5 mmol), and 2-hydroxyacetylfuran (82 mg, 0.65 mmol) in THF (1.5 mL) at –35 °C and the mixture was stirred at same temperature for 24 h. The reaction mixture was poured on to 1 M HCl and extracted with ether. The organic layer was washed with brine and dried over magnesium sulfate. Evaporation of the solvent under reduced pressure and purification of the residue by silica gel column chromatography (PE–EtOAc 1:1) afforded the aldol adduct (102 mg, 0.45 mmol, 90 %, d.r. 6:1, major = 96 % ee, minor = 70 % ee). The compound was purified by silica gel column chromatography (PE–EtOAc 3:2). Major diastereomer (less polar isomer): t_r = 7.44 min (major enantiomer) and 10.43 min, (Chiralcel OD, λ = 254 nm, heptane–isopropanol 90:10, 1 mL min^{–1}). mp 77 °C, $[\alpha]_D^{25}$ –2.76 (c = 3.0, CHCl_3 , 91 % ee). IR (KBr) ν cm^{–1}: 3457, 3060, 2920, 2850, 1682, 1599, 1578, 1449, 1395, 1257, 1119, 1037. ¹H NMR (300 MHz, CDCl_3): δ 7.86 (d, J = 7.1 Hz, 2H), 7.62 (t, J = 7.3 Hz, 1H), 7.50 (t, J = 7.1 Hz, 2H), 5.22 (dd, J = 5.1 Hz, 1.2 Hz, 1H), 3.99 (d, J = 5.1 Hz, 1H), 3.58 (td, J = 9.0 Hz, 1.2 Hz, 1H), 2.08–0.88

(m, 11H), 1.88 (d, $J=10.3$ Hz, 1H). ^{13}C NMR (75 MHz, CDCl_3): δ 200.8, 133.9, 133.6, 128.9, 128.4, 77.0, 73.2, 41.3, 29.4, 29.3, 26.3, 25.9, 25.8. Anal. Calcd for $\text{C}_{15}\text{H}_{20}\text{O}_3$: C, 72.55; H, 8.12. Found: C, 72.74; H, 8.05. Minor diastereomer (more polar isomer): $t_r=8.54$ min and 9.77 min, (Chiralcel OD, $\lambda=254$ nm, heptane–isopropanol 90:10, 1 mL min^{-1}).

General Procedure for the Proline-catalyzed Aldol Addition Reactions [16c]

To a mixture of anhydrous dimethyl sulfoxide (4 mL) and ketone donor (1 mL) was added the corresponding aldehyde (0.5 mmol) followed by L-proline (20–30 mol%) and the resulting mixture was stirred at room temperature for 4–72 h. The reaction mixture was treated with saturated ammonium chloride solution, the layers were separated, and the aqueous layer was extracted several times with ethyl acetate, dried with anhydrous MgSO_4 , and evaporated. The pure aldol products were obtained by flash column chromatography (silica gel, mixture of hexanes and ethyl acetate).

1.1.3.2 Michael Addition Reaction

Yoshitaka Hamashima and Mikiko Sodeoka

1.1.3.2.1 Introduction and Fundamental Examples

The conjugate addition of carbon nucleophiles to electron-deficient olefins, the so-called Michael reaction, is one of the most important carbon–carbon bond-forming reactions, because it is applicable to the synthesis of a wide range of compounds with various functional groups. Catalytic C–H activation of nucleophiles enables complete assembly between a Michael donor and an acceptor. In contrast with the use of organometallic reagents, such direct addition of pro-nucleophiles without stoichiometric pre-activation of the Michael donor is quite atom-economical, and is environmentally benign. Great efforts have been made to develop an asymmetric version of this attractive C–H transformation, and some reactions have reached the stage of practical use [1]. In this chapter, representative examples of catalytic enantioselective Michael reactions are collected according to the reaction type, as defined below, highlighting the key intermediates in each reaction.

With respect to the site at which the new asymmetric carbon center is created, the catalytic enantioselective Michael reaction can be categorized into two groups (Fig. 1): in Type I an asymmetric center is generated on the Michael donor side; in Type II an asymmetric center is generated on the Michael acceptor side.

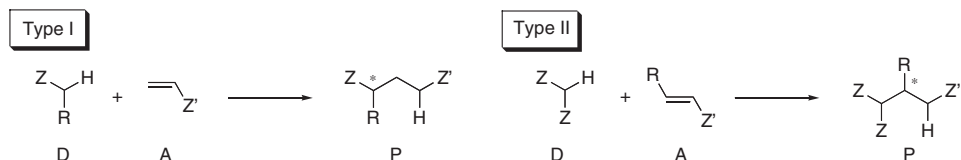


Figure 1. Types of enantioselective Michael reaction.

In addition to the structure of the products, the mode of action of the catalysts is also an important consideration for classifying the Michael reaction. For Type I reactions, most catalysts are expected to interact with the Michael donor to give a chiral nucleophile (Type A). On the other hand, in Type II reactions, the catalysts are thought to play a role in defining the position of the Michael acceptor (Type B). Recently, bifunctional catalysis, in which the same catalyst both activates the starting materials and defines their orientation, has emerged as a powerful strategy (Type C). Many catalyst systems have been reported, and these can be divided into groups (Fig. 2). For Type I reactions there are: (1) basic catalysts, (2) transition metal complexes, and (3) organic catalysts that give a chiral enamine. For Type II reactions there are: (4) chiral Lewis acid catalysts including heterobimetallic complexes and (5) organic catalysts to activate the Michael acceptors.

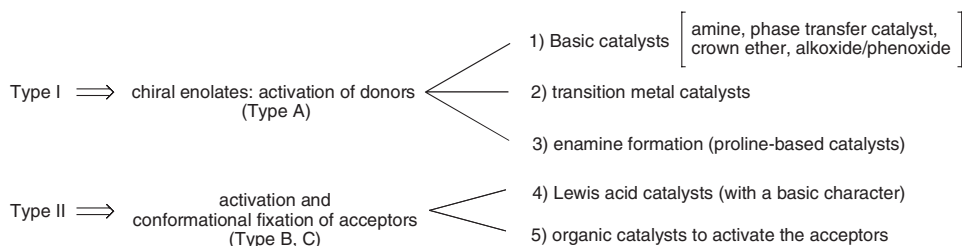
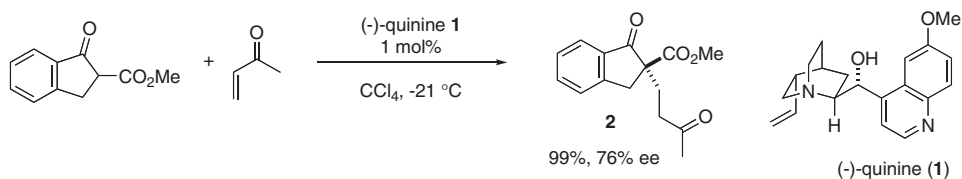


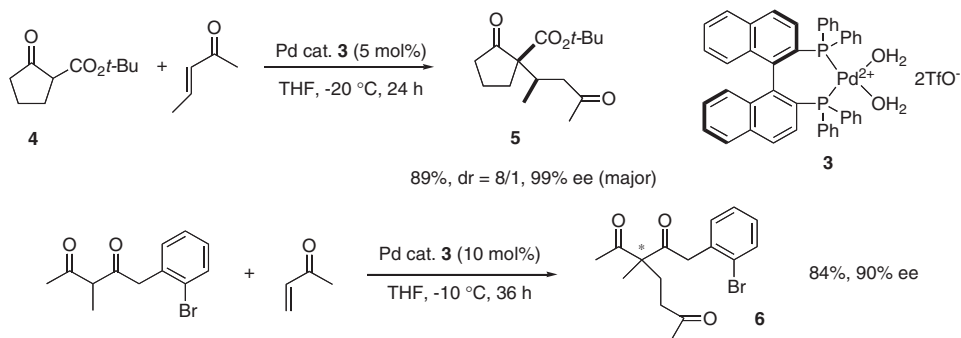
Figure 2. Types of catalyst for enantioselective Michael reactions.

The most frequently used Michael donors are stabilized carbanions, in particular enolate derivatives, which are derived from readily enolizable compounds such as β -ketoesters. The desired C–H transformation can be initiated by abstraction of an acidic proton. Accordingly, naturally occurring amines were examined as the chiral base in early work. As for the Type I reactions, after the first report by Långström and Bergson [2], Wynberg et al. examined a series of cinchona alkaloids systematically, and (–)-quinine **1** was found to catalyze the reaction of indanone 2-carboxylate with methyl vinyl ketone to afford the Michael adduct **2** in 76 % ee (Scheme 1) [3]. This reaction has since been widely used as a model reaction. Surprisingly, although various kinds of catalyst, including chiral crown ethers, alkoxides, and transition metal complexes [4], have been examined, expanding the scope of the reaction of β -ketoesters has been difficult until quite recently.



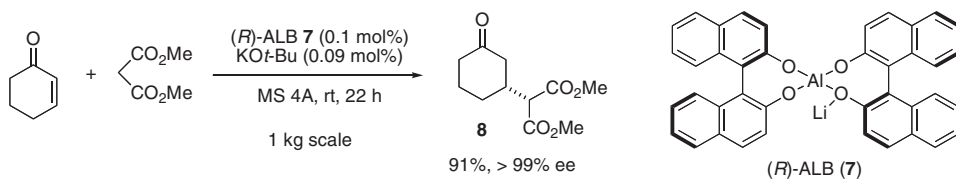
Scheme 1. Catalysis of the reaction of indanone 2-carboxylate with methyl vinyl ketone to afford Michael adduct **2**

In contrast with previous reports, Sodeoka's reaction conditions were applicable to a variety of β -ketoesters (Scheme 2) [5]. With the Pd aqua complex **3**, the Michael adducts were obtained in high yield with high enantioselectivity. For example, the reaction of the β -ketoester **4** with less reactive β -substituted enones such as 3-penten-2-one proceeded smoothly to give **5** in 99% ee. In this reaction, catalytic asymmetric construction of the highly crowded vicinal tertiary and quaternary carbon centers was achieved in one step. Furthermore, the reaction of 1,3-diketones with enones was successfully performed, and the desired triketone **6** was obtained in good yield and with 90% ee. In contrast, conventional basic conditions (tertiary amines, alkoxides, or ammonium hydroxides) gave complex mixtures, probably because of the instability, under the basic conditions, of the triketone produced. This result clearly indicates that the reaction using the Pd aqua complex **3** is quite mild.



Scheme 2. Sodeoka's reaction of β -ketoesters.

Catalytic enantioselective conjugate addition to prochiral acceptors, the Type II reaction, is also synthetically useful. Among reported examples, the heterobimetallic complexes developed by Shibasaki and Sasai are highly efficient in the reaction of cyclic enones with malonates; this represents the current state of the art in the field of asymmetric catalysis [6a]. These complexes are composed of two distinct metal cations, one of which is a group 3 (lanthanides) or group 13 (Al, Ga) metal as a Lewis acid, and the other is an alkali metal as a basic moiety, and several binaphthoxides as chiral ligands. Among these, the ALibis(binaphthoxides) (ALB) complex **7** is the most efficient (Scheme 3) [6b]. This catalyst is applicable to

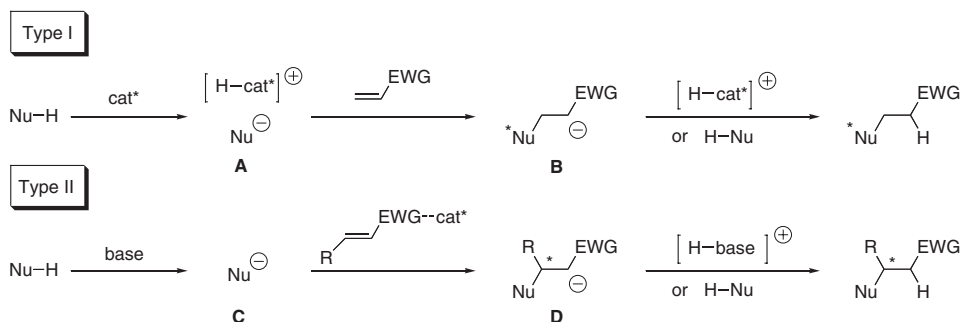


Scheme 3. Use of ALB catalyst (**7**) in the preparation of **8**.

a large-scale synthesis [6c]. For instance, the reaction of cyclohexenone with dimethyl malonate was carried out on a kilogram scale using 0.1 mol% of **7**, and the desired product **8** was obtained in 91 % yield by simple recrystallization.

1.1.3.2.2 Mechanism

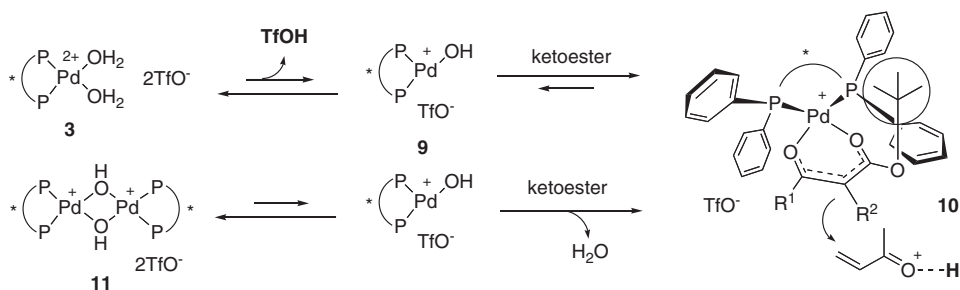
The general reaction mechanism of the Michael reaction is given below (Scheme 4). First, deprotonation of the Michael donor occurs to form a reactive nucleophile (**A**, **C**). This adds enantioselectively to the electron-deficient olefin under the action of the chiral catalyst. In the final step, proton transfer to the developed enolate (**B**, **D**) occurs from either a Michael donor or the conjugate acid of a catalyst or a base, affording the desired Michael adduct. It is noteworthy that the large difference of stability between the two enolate anions (**A/B**, **C/D**) is the driving force for the completion of the catalytic cycle.



Scheme 4. Mechanism of the Michael reaction.

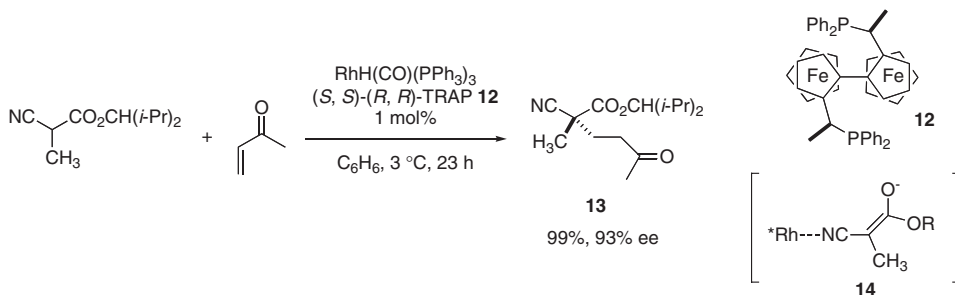
For better understanding it is necessary to consider the key intermediate which controls the enantioselection step more carefully. In Type I reactions, discrimination of the enantiofaces of the enolate is required. Therefore, the formation of the chiral enolate complex is a significant step in achieving high enantiocontrol. In transition metal-catalyzed reactions, the chiral enolates can be formed in several ways. In Sodeoka's reaction (Scheme 2), it was proposed that the in situ-generated Pd hydroxo complex **9** would react with an active methine compound to form the chiral palladium enolate **10**, and this was confirmed by NMR studies and ESI mass spectroscopy (Scheme 5). This enolate, which was prepared separately by reaction with the Pd(μ -OH) complex **11**, was not sufficiently reactive with enones in itself. In contrast, reactions using the Pd aqua complexes proceeded smoothly. These results indicated that the enone was activated by a protic acid (TfOH), which was generated concomitantly during the formation of the Pd enolate from **3**. It is interesting that the strong protic acid and inherently basic Pd enolate seem to act cooperatively to promote the C–C bond-forming reaction. Moreover, the absolute configuration of the products was in accord with the prediction based on the configurationally stable Pd enolate **10**. Interestingly, similar metal enolates

had been proposed as key intermediates elsewhere, although little experimental evidence was offered [4c–h].



Scheme 5. Formation of a chiral palladium enolate in Sodeoka's reaction.

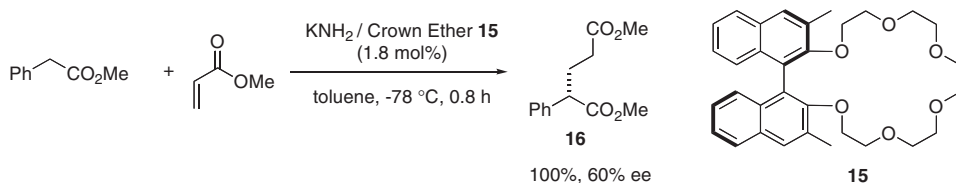
Another impressive example of the transition metal-catalyzed Michael reaction was reported by Sawamura and Ito in 1992 (Scheme 6) [7]. α -Methylcyanoacetate was treated with enones using 1 mol% Rh-TRAP (**12**) complex, and the corresponding adduct **13** was formed in up to 93 % ee. For this reaction, the trans-coordination mode of the chiral diposphine **12** was essential for high asymmetric induction. It was proposed that coordination of the nitrile group to Rh, then oxidative addition of the active methine C–H bond gave not the α -C-bound enolate, but the nitrile-coordinating enolate **14**, which was considered to be a reactive intermediate. The unique structure of this enolate was supported by X-ray analysis of a similar achiral Ru–cyanoacetate complex [8].



Scheme 6. The Sawamura and Ito transition metal-catalyzed Michael reaction.

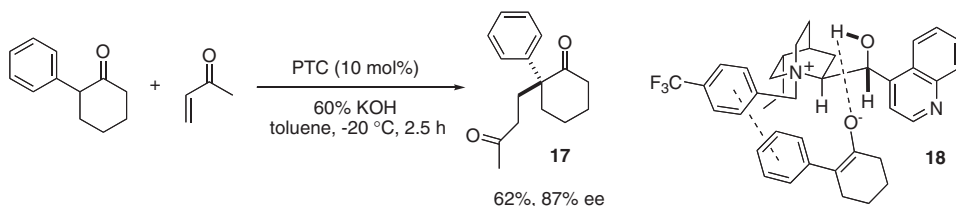
In addition to highly acidic pronucleophiles, the scope of available Michael donors was expanded to less acidic monocarbonyl compounds by introducing a more basic catalyst. In 1981, Cram et al. reported a thought-provoking example (Scheme 7) [9a]. A complex of the designed chiral crown ether **15** with KNH_2 was sufficiently basic, and reaction of phenylacetic acid ester with methyl acrylate was complete within 1 h, affording the corresponding diester **16** in 60 % ee. When 2-phenylpropionic acid ester was used, an ee of 83 % was recorded under similar reaction conditions. After this report, various crown ether complexes were examined for this reaction [9b]. These crown ethers would hold a metal enolate through

the strong chelating effect of the oxygen functionality to provide the chiral environment around the enolate.



Scheme 7. Use of crown ether as catalyst in the Michael reaction.

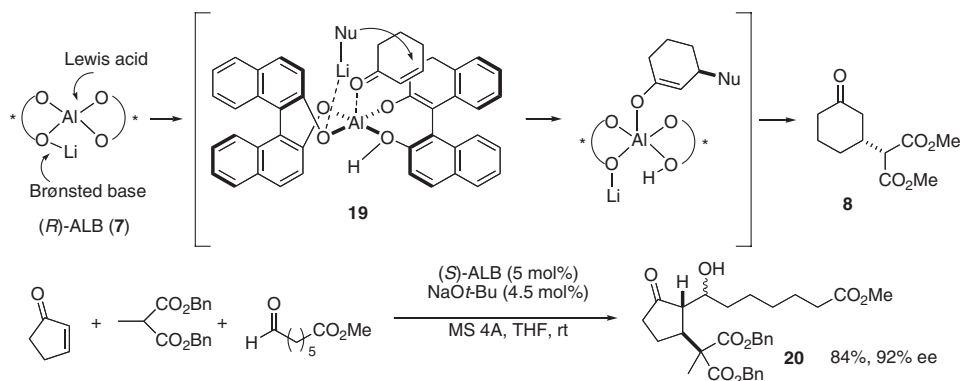
When chiral amines or phase-transfer catalysts are used, nonbonding interactions between the enolate and the catalyst must be operative. In addition to the attractive electrostatic interaction, several factors such as hydrogen bonding, van der Waals interaction, and steric repulsion should be considered. For example, on the basis of the findings by researchers at Merck [10a], Vandewalle converted 2-phenylcyclohexanone to the corresponding adduct **17** in 87% ee using a phase-transfer catalyst (Scheme 8) [10b]. The high asymmetric induction observed in this reaction was explained by assuming that the enolate complex **18** was stabilized by hydrogen bonding and π – π interaction. Thus, the two faces of the enolate were effectively differentiated, and the enone was attacked preferentially from the front to give **17**.



Scheme 8. Use of phase-transfer catalyst in the Michael reaction.

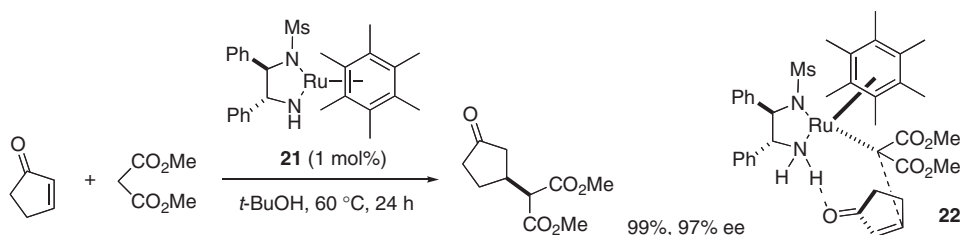
Next, the mechanism of the Type II reactions is discussed. To discriminate one of the enantiofaces of the acceptor it is desirable to place and to activate the electrophiles in a chiral environment. At the same time, effective activation of the Michael donor is required. In Shibasaki's ALB-catalyzed reaction (Scheme 3), it was proposed that the aluminum cation functioned as a Lewis acid to activate enones at the center of the catalyst, and that the Li-naphthoxide moiety deprotonated the α -hydrogen of malonate to form the Li enolate (Scheme 9). Such simultaneous activation of both reactants at precisely defined positions became feasible by using multifunctional heterobimetallic complexes; the mechanism is reminiscent of that which is operative in the active sites of enzymes. The observed absolute stereochemistry can be understood in terms of the proposed transition state model **19**. Importantly, addition of a catalytic amount of KO t -Bu (0.9 equiv. to ALB) was effective in acceleration of the reaction rate with no deterioration of the

stereoselectivity. This can be explained by the rapid formation of a tight complex of the malonate K-salt with ALB. Another unique feature of this system is the three-component coupling reaction [6d]. The Al-enolate generated by the Michael addition underwent subsequent aldol reaction, and the Michael-aldol adduct **20** was obtained with high enantioselectivity (92 % ee). This method was successfully applied to catalytic asymmetric synthesis of prostaglandin derivatives. Inspired by Shibasaki's excellent work, other heterobimetallic complexes (Ni–Cs, La–Na, and Al–Li) have also been examined for this reaction [11].



Scheme 9. Mechanism of Shibasaki's ALB-catalyzed reaction.

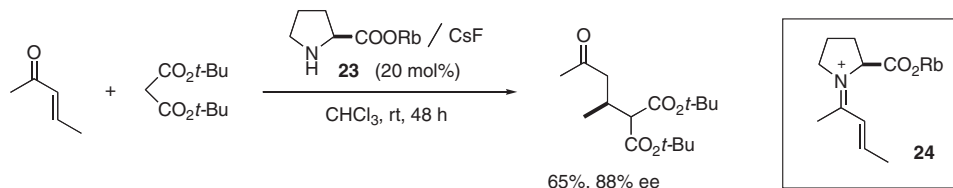
Another mechanistically interesting example was reported by Ikariya et al. in 2003 (Scheme 10) [12]. The authors focused on the basic character of the Ru-amido complex **21**. The reaction of dimethyl malonate with **21** afforded a C-bound Ru-enolate, the structure of which was supported by X-ray analysis. It was considered that the N–H moiety plays a role in bringing the enones to the optimum position by hydrogen bonding, as shown in **22**; C–C bond formation then occurs at relatively high reaction temperature, affording the desired adduct in 97 % ee. Before this report appeared, a related catalyst system had been examined by Suzuki et al. for the Type I reaction [4f].



Scheme 10. Ikariya reaction of dimethyl malonate.

Activation of enones by formation of an iminium cation is an interesting strategy that has been highlighted for organocatalysis in recent publications. A similar concept has been investigated for the enantioselective Michael reaction of malo-

nates and/or nitroalkanes to enones using the L-proline Rb salt **23** developed by Yamaguchi et al. (Scheme 11) [13]. This catalyst seemed to behave completely differently from the previously mentioned chiral amine catalysts. Reversible formation of the iminium cation **24** from the secondary amine and the acceptor was proposed as the critical step.

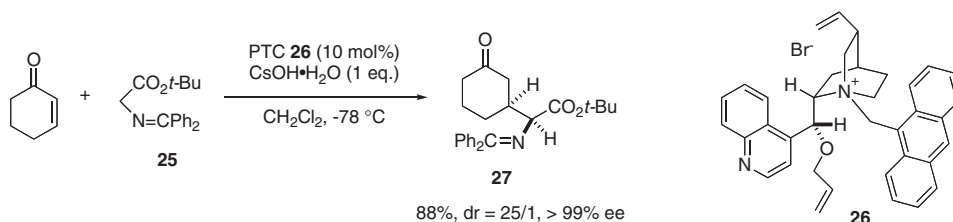


Scheme 11. Michael reaction of malonates with enones using the L-proline Rb salt.

1.1.3.2.3 Scope and Limitations

If a greater range of substrates could be used, the synthetic utility of the Michael reactions would be significantly enhanced. For this reason several new catalytic systems have been developed, and the scope of the Michael reaction is becoming rather broad. In this following section, selected examples are briefly described.

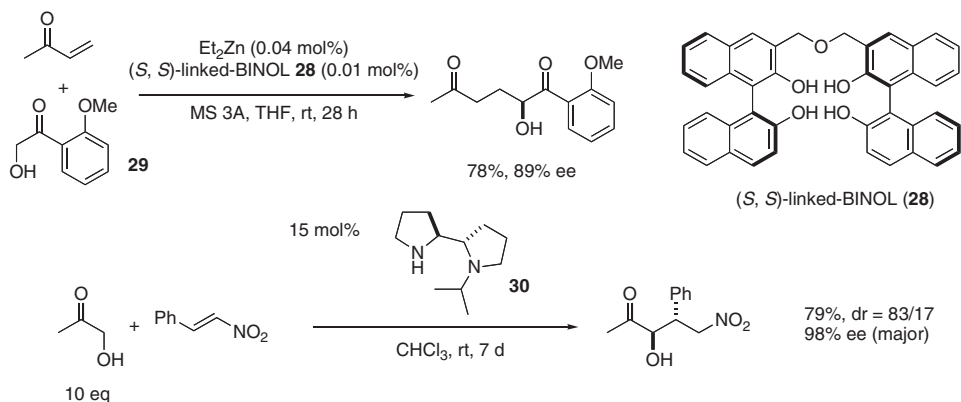
Corey demonstrated that the glycine derivative **25** was also a good Michael donor [14]. For example, **25** reacted with cyclohexenone smoothly in the presence of the chiral cinchonidium salt **26** as a phase-transfer catalyst (Scheme 12). The corresponding product **27** was obtained with extraordinary selectivity (*dr* = 25:1, >99% ee). Restricting the conformation of the ammonium cation by attaching the 9-anthracenylmethyl group to the bridgehead nitrogen presumably fixed the location of the enolate oxygen. This effect, coupled with the attractive van der Waals interaction, led to the formation of a tight ion pair with extremely stable geometry. The high enantioselectivity observed can be well explained by involvement of such a well-defined enolate complex.



Scheme 12. Use of glycine derivative **25** as Michael donor.

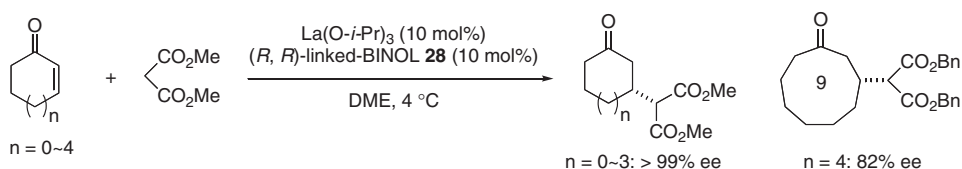
A multinuclear Zn-binaphthoxide complex prepared from Et_2Zn and the linked-BINOL **28** has recently been developed as an effective catalyst for the Michael reaction (Scheme 13) [15]. The α -hydroxy acetophenone derivative **29** was a suitable substrate, reacting with the Zn complex to afford the configurationally stable Zn enolate. Reaction with a variety of enones proceeded smoothly and

highly enantioselectively (up to 99 % ee). Interestingly, the amount of catalyst could be reduced to 0.01 mol%, while maintaining a reasonably high level of asymmetric induction (89 % ee, TON = 7800). A structurally related, but mechanistically distinct, reaction of α -hydroxy acetone with nitroolefin was reported by Alexakis et al [16]. The proline-derived secondary amine **30** reacted with the donor to form a chiral enamine intermediate, which was attacked with up to 98 % ee.



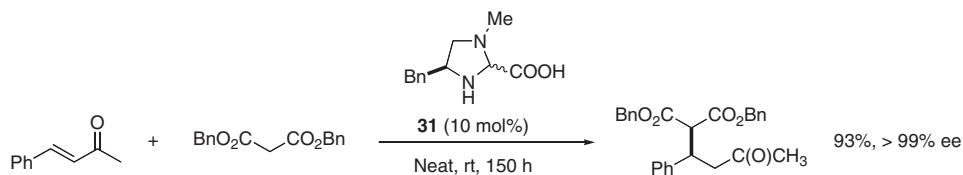
Scheme 13. Use of α -hydroxy ketones in the Michael reaction.

For Type II reactions also a variety of useful compounds can be synthesized by changing the combination of the starting materials. In the Michael reaction with cyclic enones, availability of the La-linked-BINOL complex broadened the scope of the Michael acceptor (Scheme 14). It should be noted that less reactive medium-ring-size cyclic enones (7–9 membered ring size) underwent conjugate addition highly enantioselectively (up to > 99 % ee) [17].



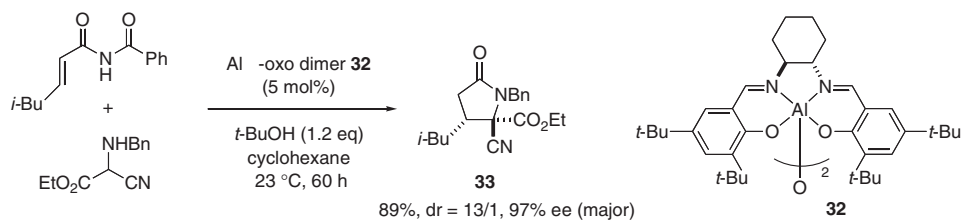
Scheme 14. Use of the La-linked-BINOL complex in the Michael reaction with cyclic enones.

A new chiral secondary amine **31** developed by Jørgensen et al. was introduced as a general catalyst for the Michael reaction of acyclic enones (Scheme 15). Although a relatively long reaction time and excess malonate were required for completion of the reaction, high enantioselectivity of up to 99 % was usually obtained [18]. When β -ketoesters were used in place of malonates, intramolecular aldol addition occurred after conjugate addition, giving highly stereocontrolled cyclohexanone derivatives. It is likely that **31** acts in a similar manner to Yamaguchi's proline Rb catalyst, affording the iminium intermediate to enhance the electrophilicity of enones.

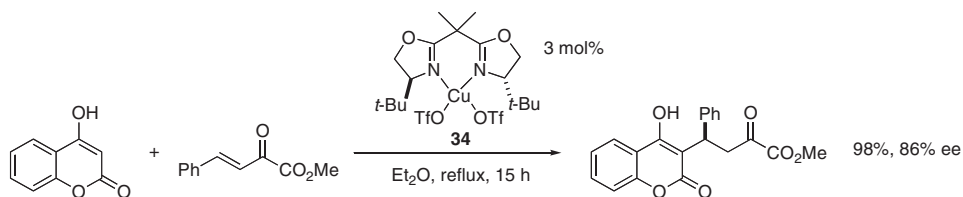


Scheme 15. Michael reaction of acyclic enones with secondary amine catalyst.

Jacobsen et al. have shown that cyanoacetate derivatives undergo conjugate addition to α,β -unsaturated imides in the presence of a chiral Al-oxo salen complex **32** to afford the corresponding product in up to 98% ee (Scheme 16) [19]. When an α -amino cyanoacetate was used, a highly functionalized lactam **33** was obtained in one step. Another example of Lewis acid-catalyzed conjugate addition of cyclic 1,3-dicarbonyl compounds to 2-oxobutenoate employed the chiral Cu-bisoxazoline complex **34** (Scheme 17) [20].

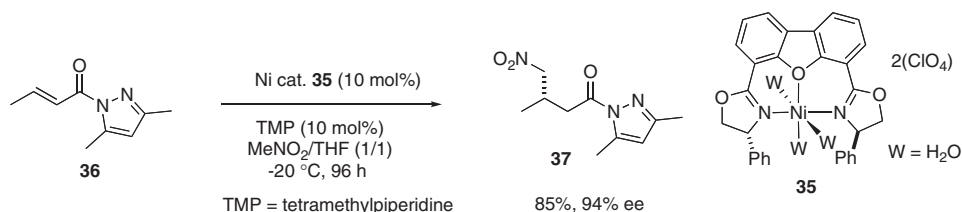


Scheme 16. Conjugate addition of cyanoacetate derivatives to α,β -unsaturated imides.



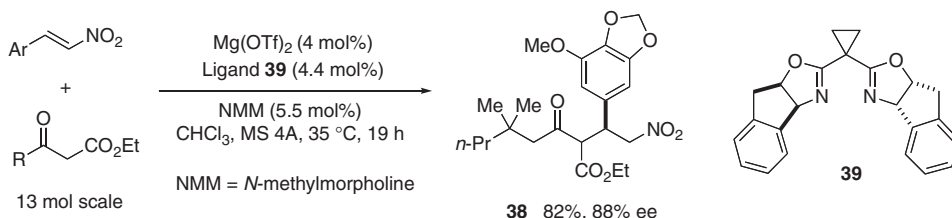
Scheme 17. Lewis acid-catalyzed conjugate addition of cyclic 1,3-dicarbonyl compounds to 2-oxobutenoate.

Nitro compounds are also useful starting materials, because a nitro group can be readily converted to a carbonyl group or to amino functionality. Addition reactions of nitroalkane have been reported by Yamaguchi [13b], Shibasaki [6a], Bakó and Töke, Corey, Hanessian, and Kanemasa [21]. For example, Kanemasa used their chiral Lewis acid complex **35** for the reaction of **36** with nitromethane (Scheme 18). The reaction proceeded with the aid of the amine co-catalyst, affording the product **37** with high enantioselectivity. This system was also applicable to the reaction of malononitrile [21e].



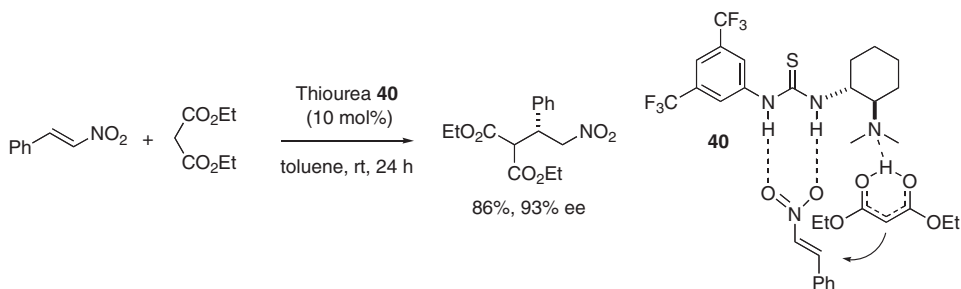
Scheme 18. Use of the Kanemasa chiral Lewis acid complex.

Nitroolefins are attractive alternative acceptors to enones. In 1999, Barnes and Ji reported an efficient catalyst system for reaction of nitroolefins with 1,3-dicarbonyl compounds with high enantioselectivity (up to 97 % ee; Scheme 19) [22]. Using this method, a highly functionalized nitro compound **38**, an important intermediate in the synthesis of an endothelin-A antagonist, was prepared on a large scale in 88 % ee. In this case, the formation of a chiral Mg enolate as a reactive intermediate was proposed.



Scheme 19. Catalytic reaction of nitroolefins with 1,3-dicarbonyl compounds.

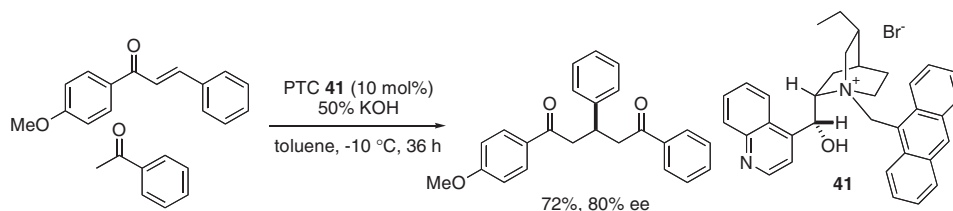
For similar reactions, Takemoto et al. developed a novel organocatalyst **40**, which was designed to place both acidic and basic moieties appropriately on the same catalyst scaffold (Scheme 20) [23]. It was proposed the thiourea activated nitroolefins by hydrogen bonding.



Scheme 20. Use of thiourea as organocatalyst in the Michael reaction.

In the same way as in Type I reactions, a simple aromatic ketone, for example acetophenone, can also be used as a Michael donor in a Type II reaction (Scheme 21). Using 50 % KOH as a base, the reaction proceeded smoothly in the

presence of **41** [24]. Although the Michael donor alone was probably fixed in the chiral environment, as already discussed, a new chiral center was created on the acceptor side with reasonably high asymmetric induction.



Scheme 21. Use of a simple aromatic ketone as a Michael donor in a Type II reaction.

In addition to the stabilized carbanions, electron-rich aromatic compounds, for example indole derivatives have emerged as new Michael donors [25]. In these reactions, aromatic sp^2 -C–H transformation is involved. These reactions are described in detail in Section III.1.3.1.3. A highly enantioselective intramolecular Stetter reaction, in which umpolung reactivity of a formyl group was accomplished using a chiral triazolium salt, has also been reported by Rovis [26].

Experimental

(1*R*,1'*R*)-*tert*-Butyl 2-oxo-1-(1'-methyl-3'-oxobutyl)cyclopentanecarboxylate (**5**)

Under a nitrogen atmosphere, [Pd((*R*)-binap)(H₂O)₂](TfO)₂ (21.3 mg, 0.02 mmol, 5 mol%) was dissolved in THF (0.1 mL). To this solution was added *t*-butyl 2-oxocyclopentanecarboxylate (75 μ L, 0.4 mmol) at ambient temperature. After cooling to -20°C , 3-penten-2-one (2 equiv., mixture with 30 % mesityl oxide) (110 μ L, ca. 0.8 mmol) was added slowly. The reaction mixture was stirred at the same temperature for 24 h and monitored by TLC (hexane–ethyl acetate, 4:1). Saturated NH₄Cl (2 mL) and water (5 mL) were successively added to the mixture for quenching. The aqueous layer was extracted with ethyl acetate (3 \times 10 mL). The combined organic extracts were washed with brine and dried over Na₂SO₄. Removal of the solvent under reduced pressure, followed by flash column chromatography (SiO₂, eluent: hexane–ethyl acetate, 10:1) afforded the desired product (major: colorless oil, 85 mg, 79.2 %; minor: colorless oil, 10.6 mg, 9.9 %). The enantiomeric excess of the major product was determined by HPLC analysis to be 99 %.

(*R*)-3-[bis(Methoxycarbonyl)methyl]cyclohexanone (**8**)

A dried 2-L round-bottomed flask containing dried powdered MS 4 Å (150 g) was purged with argon and cooled to 4°C in an ice–water bath. Dimethyl malonate (686 mL, 6.0 mol), 0.1 M THF solution of (*R*)-ALB (60 mL, 0.1 mol%), and 0.086 M THF solution of KO*t*-Bu (63 mL, 0.09 mol%) were successively added to the flask. Finally, 2-cyclohexenone (581 mL, 6.0 mol) was slowly added to the mixture within 30 min. Stirring was continued for 90 min, the ice–water bath was removed, and

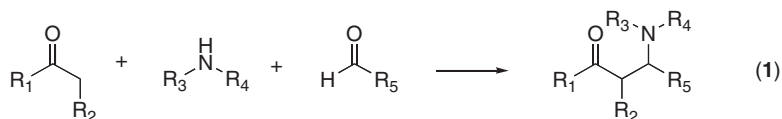
the reaction mixture was left to warm to room temperature and further stirred for 22 h. At this point, the desired Michael adduct precipitated as a white solid. The precipitate was dissolved in EtOAc (1 L) and the resulting suspension was filtered through a Celite pad, eluting with EtOAc (3×200 mL), to remove MS 4 Å. The combined organic extracts were washed with 1 M HCl (2×200 mL), saturated NaHCO_3 (200 mL), and brine (2×200 mL), dried over Na_2SO_4 , and concentrated to ca. 2 L, containing ca. 700 mL EtOAc, under reduced pressure. Hexane (3 L) was added to the residue with vigorous stirring to afford the Michael adduct (first: 1036 g) as white crystals. After the third recrystallization, the combined yield reached 91 % (1243 g). The enantiomeric excess of each crop was determined to be greater than 99 % ee.

1.1.3.3 Direct Catalytic Asymmetric Mannich Reactions

Armando Córdova

1.1.3.3.1 Introduction

The Mannich reaction is a classic method for preparation of β -amino carbonyl compounds and therefore a very important carbon–carbon bond-forming reaction in organic synthesis. The versatility and potential to create both functional and structural diversity using this reaction have long stimulated the creativity of chemists [1]. For example, it has been successfully employed numerous times as a key step in natural product synthesis and in medicinal chemistry [2]. The first asymmetric Mannich reactions were diastereoselective and involved addition of preformed enolates and enamines to preformed imines using stoichiometric amounts of chiral auxiliaries [3]. Only recently the first successful examples of catalytic asymmetric additions of enolates to imines were reported by the groups of Kobayashi [4], Sodeoka [5], and Lectka [6]. Preparation and instability of the preformed enolates used can be a disadvantage of these stereoselective Mannich reactions, however. More recently, indirect organocatalytic enantioselective Mannich-type reactions have been reported by Jacobsen and Akiyama [7, 8]. In addition, Snapper's and Hoveyda's organosilver complexes are excellent catalysts in indirect one-pot three-component asymmetric Mannich reactions [9]. The most effective and atom economic asymmetric Mannich reaction would be a catalytic process that involves the same equivalents of unmodified carbonyl donor, amine, and acceptor aldehyde (Eq. 1) [10].



Recently, direct catalytic asymmetric Mannich-type reactions were reported via C–H activation of carbonyl compounds. The transformations are catalyzed both by organometallic complexes and metal-free organic catalysts.

1.1.3.3.2 Organometallic Catalysts

Shibasaki and coworkers have conducted extensive research on the use of heterobimetallic complexes as catalysts for asymmetric synthesis [11]. The reactions are catalyzed by heterobimetallic complexes that function as both a Lewis acid and a Brønsted base. Among these, $\text{LaLi}_3\text{tris}(\text{binaphthoxide})$ catalyst **1** (LLB) was proven to be an effective catalyst in direct asymmetric aldol reactions (Fig. 1) [12]. On the basis of this research, Shibasaki et al. reported the first report of a direct catalytic asymmetric Mannich reaction [13].

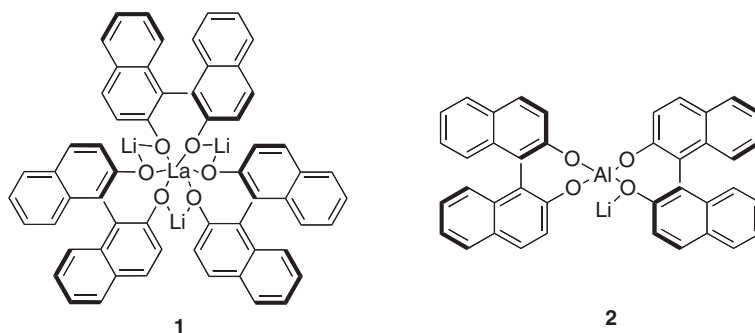
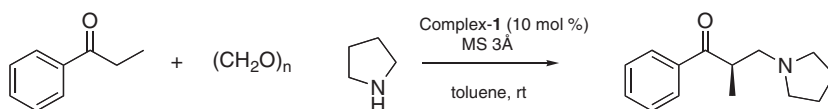


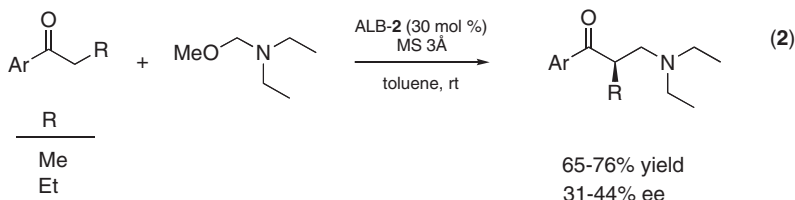
Figure 1. $\text{LaLi}_3\text{tris}(\text{binaphthoxide})$ catalyst **1** and $\text{AlLibis}(\text{binaphthoxide})$ (ALB) **2**.

In their initial one-pot three-component experiment, propiophenone, $(\text{CH}_2\text{O})_n$, and pyrrolidine were reacted in the presence of a catalytic amount of LLB, affording the corresponding Mannich product with an ee of 64 % (Scheme 1).



Scheme 1. The first direct catalytic asymmetric Mannich reaction.

The yield of the Mannich product was only 16 %, because of competing formation of $\text{C}_4\text{H}_8\text{NCH}_2\text{NC}_4\text{H}_8$. The chemoselectivity of the Mannich reaction can, however, be significantly increased by in situ generation of the iminium ion using aminomethyl ethers in combination with rare earth metal triflates and $\text{AlLibis}(\text{binaphthoxide})$ (ALB) **2** (Fig. 1) as the catalyst (Eq. 2).



The cooperative complex of ALB **2** and $\text{La}(\text{OTf})_3 \cdot n\text{H}_2\text{O}$ catalyze direct asymmetric Mannich-type reactions with good selectivity providing β -amino aryl ketones in good yields and with 31–44 % ee.

Most recently, Shibasaki et al. reported that the Et_2Zn -linked-BINOL complex **3** is an excellent catalyst for the direct asymmetric Mannich-type reaction (Fig. 2) [14, 15].

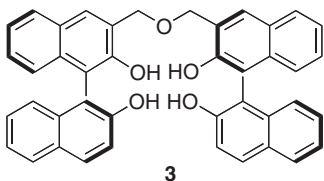
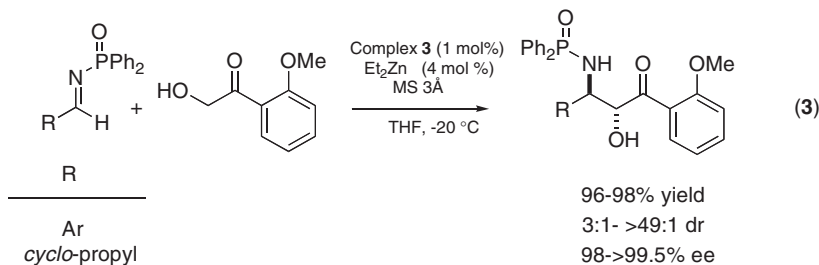


Figure 2. (*S,S*)-linked BINOL complex **3**.

The Et_2Zn /linked-complex **3** was investigated as a catalyst, because of its high selectivity in direct asymmetric syn-selective aldol reactions and Michael reactions with aryl hydroxyketones as the donors [16]. Mannich reactions between imines with different *N*-protective groups, hydroxyaceto-2-methoxyphenone, and Et_2Zn /linked complex **3**, revealed that *N*-diphenylphosphinoyl (Dpp)-protected imines were the most promising with regard to stereoselectivity. Thus, *N*-Dpp protected imines are used as acceptors and the corresponding Mannich adducts are isolated in high yields and excellent enantioselectivity (Eq. 3).



High anti-diastereoselectivity is observed for several aromatic imines; for ortho-substituted aromatic imines the two newly formed stereocenters are created with almost absolute stereocontrol. Aliphatic imines can also be used as substrates and the reaction is readily performed on the gram scale with as little as 0.25 mol% catalyst loading. Furthermore, the Mannich adducts are readily transformed to protected α -hydroxy- β -amino acids in high yield. The absolute stereochemistry of the Mannich adducts revealed that Et_2Zn -linked complex **3** affords Mannich and aldol adducts with the same absolute configuration (*2R*). However, the diastereoselectivity of the amino alcohol derivatives is anti, which is opposite to the syn-1,2-diol aldol products. Hence, the electrophiles approach the *re* face of the zinc enolate in the Mannich reactions and the *si* face in the aldol reactions. The anti selectivity is

because of the bulky Dpp group of the imine nitrogen and to avoid steric repulsion the Mannich-type reaction proceeds via the transition-state **4a** (Fig. 3a). Interestingly, changing the protective group of the preformed imines to a Boc group switched the electrophile's approach of the Zn complex **3**-derived enolate to the si face (Fig. 3b, transition state **4b**). Hence, Boc-protected syn-1,2-amino alcohols were furnished with excellent stereoselectivity (Eq. 4) [15].

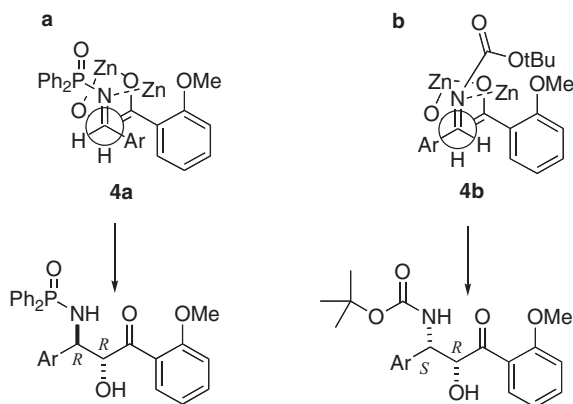
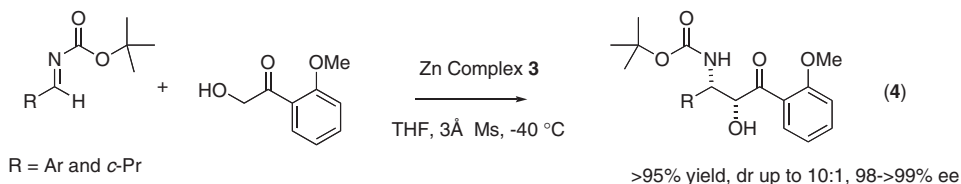
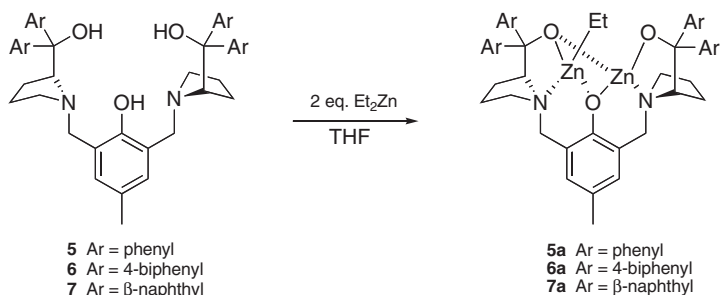


Figure 3. Plausible transition states **4a** and **4b**.

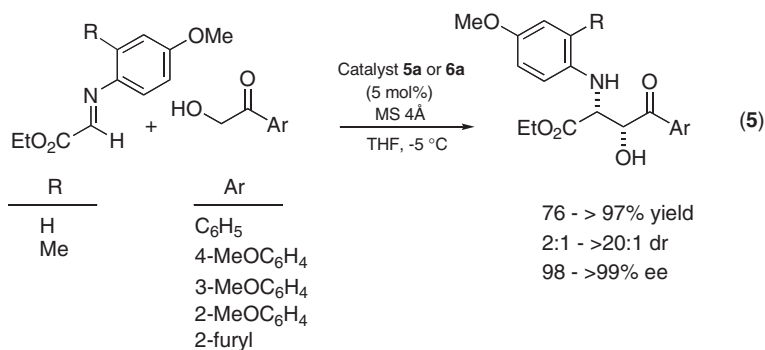


Trost et al. have discovered a novel design of dinuclear zinc catalyst that can catalyze diastereoselective and enantioselective direct aldol reactions [17]. The dinuclear zinc catalysts **5a–7a** are generated in situ by exposing the appropriate ligands **5–7**, respectively, to 2 equiv. diethylzinc in THF (Scheme 3).



Scheme 3. Generation of di-nuclear Zn catalysts **5a–7a**.

Trost and coworkers recently reported that these dinuclear zinc complexes catalyze Mannich reactions with unmodified aromatic hydroxy ketones as donors with excellent enantioselectivity [18]. Mannich-type reactions between an *N*-*para*-methoxyphenyl (PMP)-protected α -ethyl glyoxalate and hydroxyacetophenone in the presence of a catalytic amount of catalyst **5a** afford the desired *N*-PMP protected amino acid derivative in 76 % yield with a dr of 7:1 and 95 % ee (Eq. 5).



Imines derived from the more sterically demanding 2-methyl-4-methoxyaniline derivatives and ethyl glyoxylate provide even higher selectivity. A significant ligand effect is present, and when ligand **6** is used the yield and diastereoselectivity are further improved. The biphenyl ligand **6** is therefore used as the standard ligand for reactions with glyoxylate imines. The Zn₂-linked complex **6a** catalyzes Mannich reactions with more electron-rich aromatic hydroxy ketones and a single diastereoisomer is formed with *ortho*-substituted methoxy hydroxy ketone as the donor. The dinuclear zinc complex-catalyzed reactions are also highly enantioselective for acceptor imines derived from aromatic aldehydes. In this case, β -naphthyl ligand **7** significantly increases the diastereoselectivity of the reaction. The employment of *ortho*-methoxy aniline-derived acceptor imines also dramatically increases the diastereoselectivity of the reaction. This is explained by a bidentate binding model with the *ortho*-substituted derivative in which two point binding of the imine through the nitrogen and the methoxy group helps rigidify the dynamic nature of the imine–Lewis acid complex preventing *E/Z* isomerization of the carbon–nitrogen double bond. Importantly, a nearly atom-economic process can be achieved – 1.1 equiv. ketone, with no change in chemoselectivity, by addition of “zincaphilic” additives such as Ph₃PS and Ph₃AsO. The 1,2-amino alcohol derivatives are valuable synthetic intermediates. For example, a three-step procedure including Baeyer–Villiger oxidation and oxidative dearylation provides protected *syn* α -hydroxy- β -amino acids that are constituents of natural products, e.g. Taxol [2e]. NOE-experiments confirmed that *syn*-1,2-amino alcohols are formed. This is opposite to the dinuclear zinc complex-catalyzed direct asymmetric aldol reaction in which vicinal diols are obtained with an *anti* configuration [17].

Jørgensen and coworkers have developed direct asymmetric reactions catalyzed by chiral copper(II)bisoaxazoline (BOX) complexes [19]. On the basis of this

research they reported the first chiral copper(II)–(BOX) complex-catalyzed direct asymmetric Mannich reaction of activated carbonyl compounds and α -imino esters [20]. Screening of different C_2 -symmetric ligands with copper(II) as the metal ion revealed that $\text{Cu}(\text{OTf})_2/\text{BOX}$ complex **8** and **9** are catalysts in the reaction between pyruvate and N-tosyl protected α -imino ethyl glyoxylate (Fig. 4). Different α -carbonyl esters can be used as nucleophiles providing functionalized α -amino acid derivatives with excellent diastereoselectivity and enantioselectivity (Eq. 6).

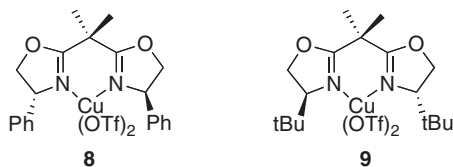
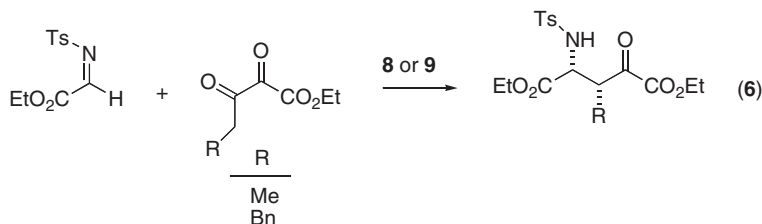


Figure 4. $\text{Cu}(\text{OTf})_2/\text{BOX}$ complex **8** and **9**.



The Mannich adducts are readily transformed to optically active α -amino- γ -lactones via a one-pot diastereoselective reduction and lactonization sequence and the tosyl group exchanged for a Boc group via a two-step procedure. The copper(II) ion is crucial for the success of this reaction [21]. It has the properties necessary both to generate the enol species in situ and, in combination with the C_2 -symmetric ligand, coordinate it as well as the imine in a bidentate fashion. The reaction proceeds via a cyclohexane-like transition state with the R substituent of the enol in the less sterically crowded equatorial position, which is required to obtain the observed diastereoselectivity (Fig. 5).

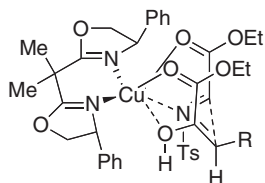
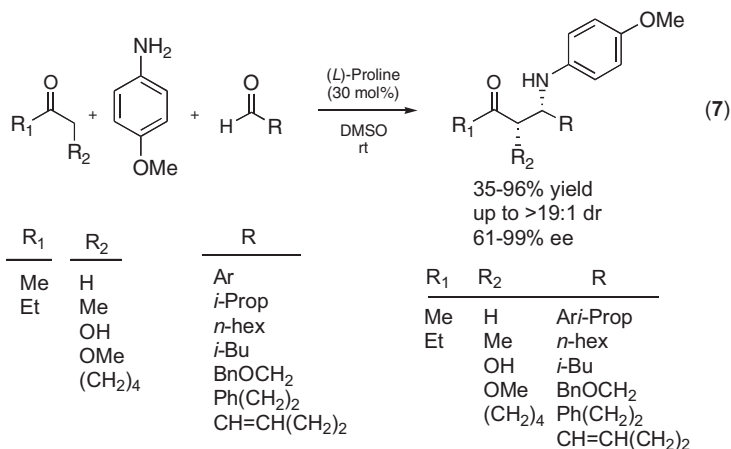


Figure 5. Plausible transition state.

The chiral $\text{Cu}(\text{OTf})_2/\text{BOX}$ complexes **8** and **9** are also catalysts of asymmetric Mannich-type additions of unmodified malonates and β -ketoesters to activated N-tosyl- α -imino esters [22].

1.1.3.3.3 Metal-free Organocatalysis

Asymmetric reactions catalyzed by metal-free organic catalysts have received increased attention in recent years [23]. Interestingly, since the discovery of amino acid-catalyzed stereoselective Robinson annulations in the early 1970s, there had been no intensive research on this concept for other C–C bond-forming reactions for several decades even though the reaction had frequently been used in the preparation of building blocks for the total synthesis of natural products [24, 25]. It was not until almost three decades later that researchers demonstrated that amino acid derivatives function as catalysts in direct asymmetric intermolecular C–C bond-forming reactions [23]. List and coworkers reported the first direct organocatalytic asymmetric Mannich reaction [26]. The design and support of such transformations were based on Kobayashi and coworkers' report of one-pot three component Mannich reactions and previous research on proline-catalyzed direct asymmetric aldol reactions [27, 28]. Hence, they envisaged that a small chiral amine would be able to form enamines with unmodified ketones and mediate stereoselective additions to in situ generated imines in one pot. The proline-catalyzed one-pot three-component reactions with acetone, *p*-anisidine, and aliphatic aldehydes proceed with excellent chemoselectivity affording Mannich adducts in high yield with 61–99% ee (Eq. 7).



The L-proline-catalyzed Mannich reaction also occurs with other ketones as donors; aliphatic ketones provide two regioisomers with good enantioselectivity. The Mannich reaction is regioselective for oxygen-substituted ketones, providing one single regioisomer in good yield with high ee. In particular, the reaction with hydroxyacetone as the donor provides a new highly chemo-, regio-, diastereo-, and enantioselective entry to chiral 1,2-amino alcohols. The highest selectivity is observed when aromatic imines with electron withdrawing groups are used as acceptors. The relative and absolute configuration was determined by X-ray analysis, confirming that syn-1,2-amino alcohols are formed. The amino alcohol products can also be converted into Boc-protected oxazolidinones in three steps, which revealed that L-proline affords β -amino ketones with the S configuration.

Barbas and coworkers later demonstrated that other amino acid derivatives in addition to proline can catalyze the direct asymmetric Mannich-type reaction with good enantioselectivity (Fig. 6) [29].

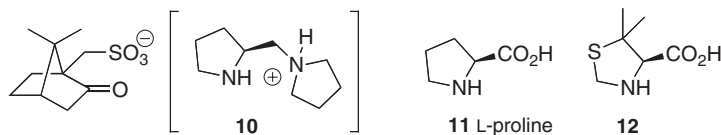
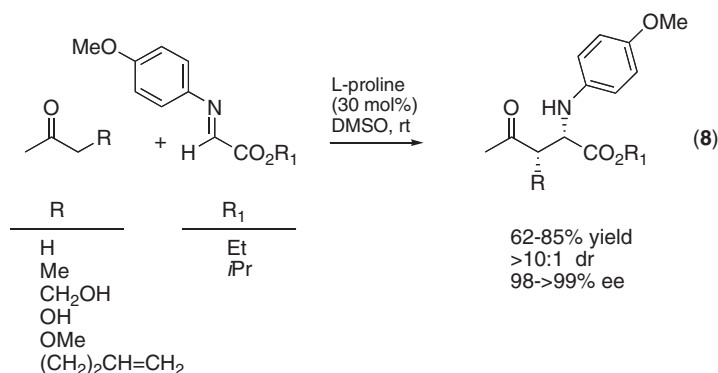


Figure 6. Organic catalysts **10**, **11**, and **12**.

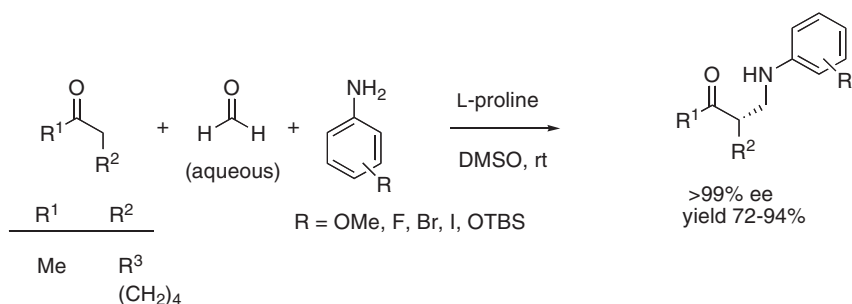
Their previous screening of catalysts for aldol reactions and Robinson annulations suggested the possibility that chiral amines might also be able to catalyze the Mannich reaction [30, 31]. Thus, screening of catalysts for Mannich-type reactions between *N*-OMP-protected aldimines and acetone revealed that chiral diamine salt **10**, L-proline **11**, and 5,5-dimethylthiazolidine-4-carboxylic acid (DMTC) **12** are catalysts of Mannich-type reactions affording Mannich adducts in moderate yields with 60–88 % ee. To extend the Mannich-type reactions to aliphatic imines, the DMTC **12**-catalyzed reactions are performed as one-pot three-component procedures. The *o*-anisidine component has to be exchanged with *p*-anisidine for the one-pot reactions to occur. The DMTC **12**-catalyzed one-pot three-component direct asymmetric Mannich reactions provide Mannich adducts in moderate yield with 50–86 % ee.

Addition of nucleophiles to electrophilic glycine templates has served as an excellent means of synthesis of α -amino acid derivatives [2c, 4–6]. In particular, imines derived from α -ethyl glyoxylate are excellent electrophiles for stereoselective construction of optically active molecules [32]. This research and retrosynthetic analysis led us to believe that amine-catalyzed asymmetric Mannich-type additions of unmodified ketones to glyoxylate derived imines would be an attractive route for synthesis of γ -keto- α -amino acid derivatives [33]. Initially, L-proline-catalyzed direct asymmetric Mannich reaction with acetone and *N*-PMP-protected α -ethyl glyoxylate was examined in different solvents. The Mannich-type reaction was effective in all solvents tested and the corresponding amino acid derivative was isolated in excellent yield and enantioselectivity (ee >95 %). Direct asymmetric Mannich-type additions with other ketones afford Mannich adducts in good yield and excellent regio-, diastereo- and enantioselectivity (Eq. 8).

The reaction is regioselective and C–C bond-formation occurs exclusively on the most substituted side of the ketone donor. In contrast, the corresponding Mannich addition of non-oxygen-substituted ketones to other imines resulted in a mixture of regioisomers [26]. The amino acid derivatives can be further manipulated and the PMP group can be exchanged for a Boc protective group via a one-pot dearylation carbamate-formation procedure without racemization. The corresponding Boc-protected γ -keto- α -amino acid derivatives are useful building blocks in peptide chemistry and medicinal chemistry. Determination of the absolute and relative configuration revealed that L-proline provides L amino acids with a syn relationship between the alkyl and amino group.



Proline and its derivatives also catalyze the “classical” asymmetric Mannich reaction between aqueous formaldehyde, anilines, and ketones. This was the first successful direct catalytic α -hydroxymethylation of ketones, and the corresponding α -aminomethyl ketones were isolated in excellent yields with up to >99% ee (Scheme 4) [34].

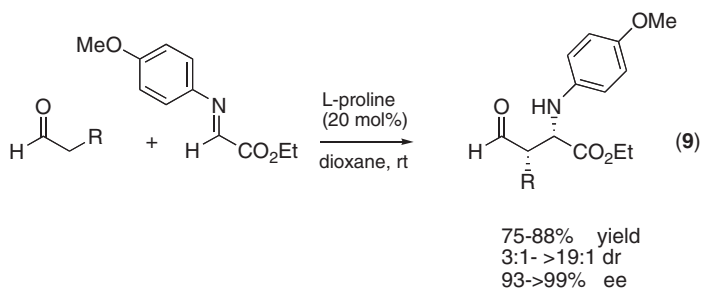


Scheme 4. Direct catalytic asymmetric “classical” Mannich reactions.

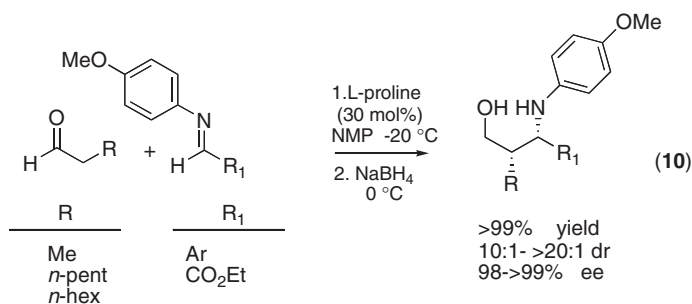
Ohsawa and coworkers have demonstrated that proline can also catalyze direct catalytic Mannich reactions between protected 3,4-dihydro- β -carbolidine and ketones, yielding indole precursors in up to 92% ee [35].

The similarity between mechanisms of reactions between proline- and 2-deoxy-ribose-5-phosphate aldolase-catalyzed direct asymmetric aldol reactions with acet-aldehyde suggests that a chiral amine would be able to catalyze stereoselective reactions via C–H activation of unmodified aldehydes, which could add to different electrophiles such as imines [36, 37]. In fact, proline is able to mediate the direct catalytic asymmetric Mannich reaction with unmodified aldehydes as nucleophiles [38]. The first proline-catalyzed direct asymmetric Mannich-type reaction between aldehydes and N-PMP protected α -ethyl glyoxylate proceeds with excellent chemo-, diastereo-, and enantioselectivity (Eq. 9).

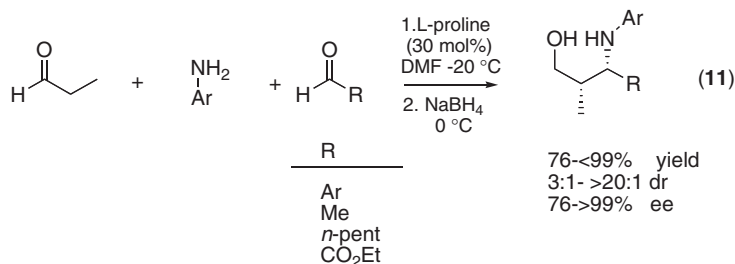
The highest enantioselectivity is achieved in dioxane, THF, DMF, and NMP (*N*-methylpyrrolidinone) affording the corresponding β -formyl functionalized amino acid derivative in high yield and stereoselectivity. The diastereoselectivity of the



Mannich reaction increases with enhanced chain-length of the donor and for aldehydes with more than six carbon atoms, the two stereocenters are formed with almost absolute stereocontrol. The reaction is readily performed on a multi-gram scale and only two equivalents of aldehyde were used and 10 mol% catalyst. Mannich-type additions with unmodified aldehydes add a new dimension to the direct asymmetric Mannich reaction, because the aldehyde moiety enables further chemical manipulations and linkage to tandem reactions to furnish functional α -amino acid derivatives and β -lactams. The absolute configuration of the *iso*-valeraldehyde-derived lactam revealed that L-proline catalyzes the creation of L-amino acid derivatives with syn relative configuration. Expansion of the proline-catalyzed cross-Mannich-type reactions to other preformed imines is also possible. The slow addition of propionaldehyde with a syringe pump to a vial containing N-PMP-protected 4-nitrobenzalimine and a catalytic amount of L-proline in DMF at 4 °C provides the desired Mannich adduct, which is reduced in situ with excess NaBH_4 to the corresponding γ -amino alcohol adduct, isolated in 81 % yield with 99 % ee [39, 40]. It is worth noting that performing proline-catalyzed Mannich-type reactions at –20 °C in DMF or NMP circumvents the use of a syringe pump and often yields the corresponding amino alcohols quantitatively and with up to >99 % ee (Eq. 10) [41].

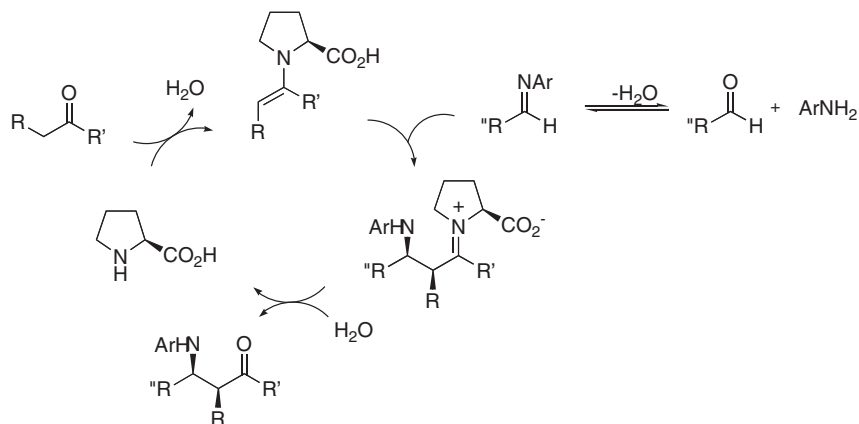


The reaction can be regarded as a regiospecific asymmetric synthesis of 3-amino-1-ols. Proline also catalyzes the first one-pot three-component direct catalytic enantioselective Mannich reactions with two unmodified aldehydes and anilines (Eq. 11) [39, 40].



The corresponding β -amino aldehydes are reduced in situ and the corresponding amino alcohols are isolated in good yield with up to >99 % ee. The Mannich reactions proceed with excellent chemoselectivity and imine formation occurs with the acceptor aldehyde at a faster rate than C–C bond-formation. Moreover, the one-pot three-component direct asymmetric cross-Mannich reaction enables aliphatic aldehydes to serve as acceptors. The absolute stereochemistry of the reaction was determined by synthesis and revealed that L-proline provides syn β -amino aldehydes with (S) stereochemistry of the amino group. In addition, the proline-catalyzed direct asymmetric Mannich-type reaction has been connected to one-pot tandem cyanation and allylation reaction in THF and aqueous media affording functional α -amino acid derivatives [39, 42].

The mechanism of proline-catalyzed Mannich reactions is depicted in Scheme 5. The ketone or aldehyde donor reacts with proline to give an enamine. Next, the preformed or in-situ-generated imine reacts with the enamine to give, after hydrolysis, the enantiomerically enriched Mannich adduct; the catalytic cycle can then be repeated.



Scheme 5. The mechanism of proline-catalyzed direct asymmetric Mannich reactions.

The stereochemical outcome of L-proline catalyzed direct asymmetric Mannich reactions is explained by a Si-facial attack on the imine, which has a trans configuration, by the Si face of the enamine, which has a trans configuration (Fig. 7).

The six-membered transition-state is stabilized by hydrogen-bonding between the nitrogen of the imine and the carboxyl group of proline. Switching of the facial selectivity is disfavored, because of to steric repulsion between the PMP group of the imine and the pyrrolidine moiety of the enamine. This is opposite to similar direct asymmetric aldol reaction in which re-facial attack occurs [27, 30, 36].

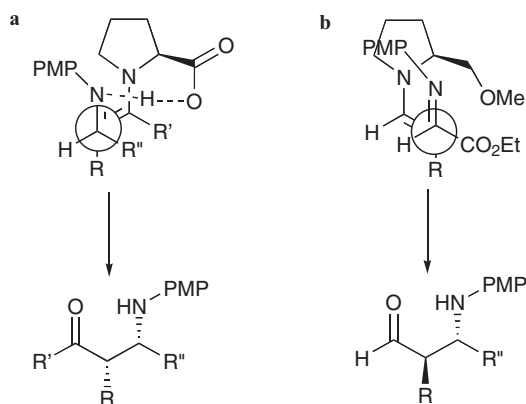
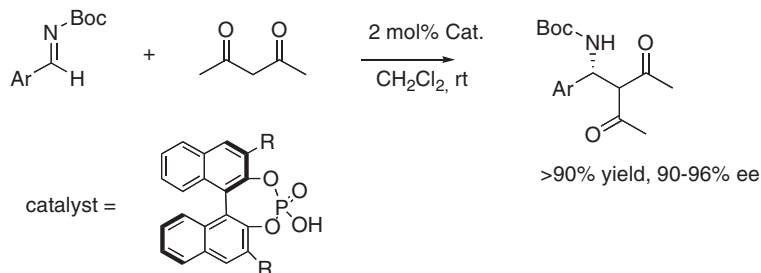


Figure 7. (a) Transition-state of the proline-catalyzed direct asymmetric Mannich reaction. (b) Transition-state of the SMP-catalyzed direct asymmetric Mannich reaction.

On the basis of previous reports of anti-selective Mannich-type reactions with preformed chiral enamines or imines, it was considered theoretically possible for a chiral amine to catalyze a similar anti-selective direct asymmetric Mannich transformation [3, 43]. Screening of chiral amines for the reaction between unmodified aldehydes and N-PMP protected α -ethyl glyoxylate revealed that ether- and ester-functionalized proline-derived secondary amines can mediate the anti-selective transformation, albeit in lower yields than proline [44]. For example, (*S*)-2-methoxymethylpyrrolidine (SMP) can catalyze the direct asymmetric Mannich reaction with high anti-selectivity, affording α -amino acid derivatives in moderate yield with 74–92% ee. The stereochemical outcome of the reaction is explained by re-face attack of the imine from the si-face of the enamine, which is the opposite to the si-facial attack of enamines derived from L-proline (Fig. 7b). In this reaction Coulombic interactions between the pyrrolidine ring and the aromatic moiety of the imine stabilize the transition-state, favoring re-facial attack. si-facial attack of the imine is less favored, because of lack of hydrogen bonding. Jørgens and coworkers have observed different facial selectivity of proline and its hydrophobic derivatives in cross-Mannich reactions with ketimines [45].

Another important means of mediation of metal-free catalytic enantioselective Mannich-type reactions is via electrophilic activation of the preformed imines by chiral Brønsted acids [7, 8, 46]. By using this strategy Terada and coworkers performed chiral phosphoric acid-catalyzed direct asymmetric Mannich-type reactions between Boc-protected imines and acetoacetone that furnished aryl β -amino

ketones with up to 96 % ee; these are readily converted to α -amino acid derivatives (Scheme 6).



Scheme 6. Chiral phosphoric acid-catalyzed direct asymmetric Mannich reactions.

Experimental

(2S)-(4-Methoxyphenylamino-methyl)cyclohexanone

To a vial containing formaldehyde (1 mmol, 36 % aqueous solution), p-anisidine (1.1 mmol), and a catalytic amount of (*S*)-proline (30 mol%) in DMSO (4 mL) was added the cyclohexanone (2 mmol). After vigorous stirring for 20 h the reaction was quenched by addition of aqueous NH_4Cl and the aqueous phase was extracted three times with EtOAc. The combined organic layers were dried with MgSO_4 , which was subsequently removed by filtration. Next, the solvent was removed under reduced pressure and the crude product mixture was purified by neutral aluminum oxide column chromatography (EtOAc–pentane, 1:10) to afford the α -aminomethylated ketone in 94 % yield as a slightly yellow solid. The ee of α -aminomethylated cyclohexanone was >99 % as determined by chiral-phase HPLC analysis. ^1H NMR (CDCl_3): δ = 1.49 (m, 2H), 1.67 (m, 2H), 2.10 (m, 2H), 2.35 (m, 2H), 3.05 (dd, J = 13.3, 9.3 Hz, 1H), 3.37 (dd, J = 12.8, 7.8 Hz, 1H), 3.74 (s, 3H), 6.63 (d, J = 8.4 Hz, 2H), 6.77 (d, J = 8.4 Hz, 2H); ^{13}C NMR: δ = 25.1, 28.0, 32.3, 42.5, 45.6, 50.0, 56.1, 114.9, 115.18, 142.2, 152.6, 213.56; HPLC (Daicel Chiralpak AD, hexanes–*i*-PrOH, 96:4, flow rate 0.5 mL min $^{-1}$, λ = 254 nm): major isomer: t_R = 44.31 min; minor isomer: t_R = 58.79 min; $[\alpha]_D$ = +4.1 (c = 2.0, CHCl_3); MALDI-TOF MS: 256.1008; $\text{C}_{14}\text{H}_{19}\text{NO}_2$ ($M + \text{Na}^+$: calcd 256.1313).

1.1.4

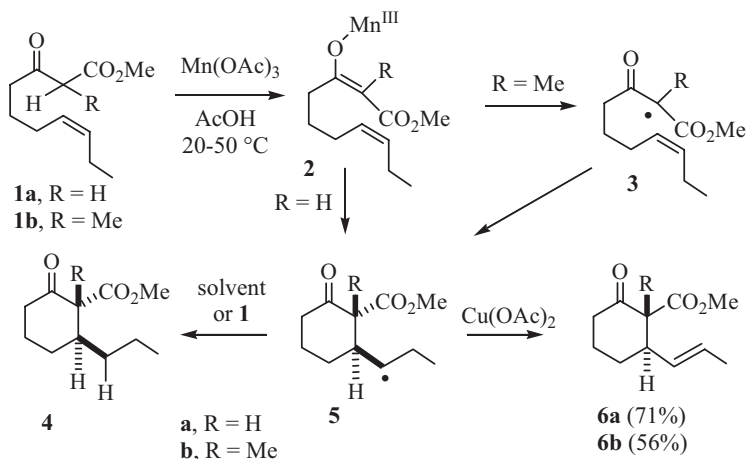
Oxidative Free-Radical Cyclizations and Additions with Mono and β -Dicarbonyl Compounds

Barry B. Snider

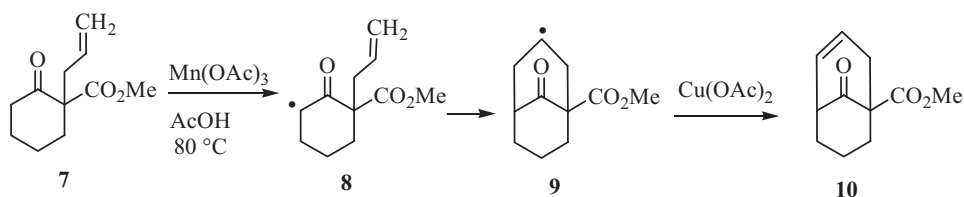
1.1.4.1 Introduction and Fundamental Examples

The reaction of β -dicarbonyl compounds and simple ketones with $\text{Mn}(\text{OAc})_3$ or ceric ammonium nitrate is a general and effective method for C–H activation that has been extensively reviewed [1–6]. The oxidative free-radical cyclizations of **1a**

and **1b** shown in Scheme 1 serve to introduce the factors that need to be understood if these reactions are to be used in synthesis. Oxidative cyclization of **1a** with 2 equiv. of $\text{Mn}(\text{OAc})_3$ and 0.1–1 equiv. of $\text{Cu}(\text{OAc})_2$ in acetic acid affords 71 % of **6a**. The analogous oxidative cyclization of **1b** provides 56 % of **6b**. β -Keto esters have been used extensively for $\text{Mn}(\text{III})$ -based oxidative cyclizations and react with $\text{Mn}(\text{OAc})_3$ at room temperature or slightly above. They may be cyclic or acyclic and may be α -unsubstituted or may contain an α -alkyl or chloro substituent [5–7]. Cycloalkanones are formed if the unsaturated chain is attached to the ketone. γ -Lactones are formed from allylic acetoacetates [5, 6]. Less acidic β -keto amides have seen limited use for the formation of lactams or cycloalkanones. Malonic esters have also been widely used and form radicals at 60–80 °C. Meldrum's acid derivatives react at room temperature [8]. Cycloalkanes are formed if an unsaturated chain is attached to the α -position. γ -Lactones are formed from allylic malonates [5, 6]. β -Diketones have been used with some success for cyclizations to both alkenes and aromatic rings [5, 6]. Other acidic carbonyl compounds, for example β -keto acids, β -keto sulfoxides, β -keto sulfones, β -nitro ketones, and β -nitro esters have seen limited use [5, 6, 9]. Oxidative cyclizations of unsaturated ketones can be performed in high yield in acetic acid at 80 °C if the ketone selectively enolizes to one side and the product cannot enolize, as shown in Scheme 2 [10].



Scheme 1. Oxidative cyclization of **1a** and **1b** showing mechanistic distinctions.



Scheme 2. Oxidative cyclization of monocarbonyl compounds.

1.1.4.2 Mechanism

These reactions have three distinct steps. The first is oxidative generation of the radical; this occurs by two distinct pathways, depending on the relative acidity of the α -protons and the ease of oxidation of the resulting enolate. The first step in the reaction is always loss of a proton to give the Mn(III) enolate, as in the formation of **2**. The next, rate determining, step of the reaction with enolates that have a high oxidation potential, such as **1a**, involves cyclization of the unsaturated Mn(III) enolate **2a** to give cyclic radical **5a**. This is the operative pathway for R=H. For substrates, such as **1b**, that are less acidic and/or give enolates that have a lower oxidation potential, loss of Mn(II) from enolate **2b** occurs rapidly to give the Mn-free free radical **3b**. In these cases, enolization of **1** is the rate determining step.

When a true free radical, such as **3b** or **5a**, is formed, it reacts further following the normal pattern of radical reactions [11]. For instance, radical **3b** cyclizes from the conformation shown to give radical **5b** stereo- and regioselectively. In appropriately designed systems it is possible to perform tandem, triple, and even quadruple cyclizations [12–14].

Finally, the cyclic or polycyclic radical must be converted to the final product. Tertiary radicals are oxidized to cations by Mn(OAc)₃. Primary and secondary radicals, such as **5**, are not oxidized by Mn(III). Heiba and Dessau found that Cu(OAc)₂ oxidizes secondary radicals 350 times faster than Mn(OAc)₃ does and that the two reagents can be used together [15]. Cu(OAc)₂ reacts with radical **5** to give a Cu(III) intermediate that undergoes oxidative elimination to give **6** and Cu(OAc). Cu(OAc) is reoxidized to Cu(OAc)₂ by Mn(OAc)₃, so these reactions are catalytic in Cu(OAc)₂ and require two equivalents of Mn(OAc)₃. Cu(OAc)₂ oxidizes secondary radicals to give primarily *E*-alkenes and the less substituted double bond (Hofmann elimination product) [16]. This selectivity is synthetically valuable, because Cu(II) oxidation of primary and secondary radicals formed in oxidative cyclizations often gives primarily or exclusively a single regio- and stereoisomer.

Cyclic radicals such as **5** can be trapped by a variety of other reagents. Use of LiCl leads to chlorides [17]. Reaction in the presence of CO results in trapping of the radical with CO to give an acyl radical that is rapidly oxidized to an acyl cation, which is trapped by the solvent [18]. Occasionally the radical can be trapped with oxygen [19]. Finally, the radical can be trapped with azide anion to give the alkyl azide, thereby providing an effective means of introducing nitrogen into the products [20].

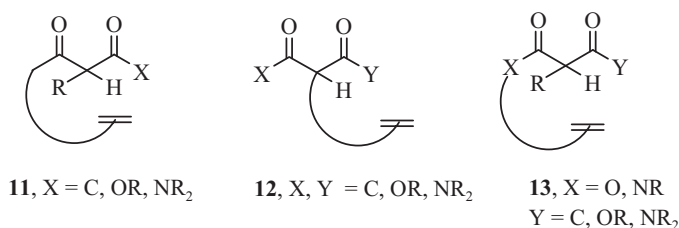
Commercially available Mn(OAc)₃·2H₂O has been used for most oxidative cyclizations. This reagent can also be prepared easily from potassium permanganate and manganous acetate in acetic acid [1]. Anhydrous Mn(OAc)₃ is slightly more reactive than the dihydrate. Reaction times with the anhydrous reagent are usually somewhat shorter but the yields of products are usually comparable. Both trifluoroacetic acid and potassium or sodium acetate have been used with Mn(OAc)₃. Use of trifluoroacetic acid as a co-solvent usually increases the rate of the reaction, but often reduces the yield of products. Acetate anion may accelerate enolization

and act as a buffer. Addition of lanthanide triflates improves the rate and selectivity of cyclizations of some β -keto esters [21].

Acetic acid is the usual solvent for $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ reactions. DMSO, ethanol, methanol, dioxane, acetonitrile, and trifluoroethanol can also be used, although higher reaction temperatures are required and lower yields of products are sometimes obtained. The use of ethanol can be advantageous in cyclizations to alkynes [22]. Vinyl radicals formed by cyclization to alkynes are not readily oxidized by $\text{Mn}(\text{III})$ and will undergo undesired side reactions unless there is a good hydrogen donor available. Ethanol acts as a hydrogen donor, reducing the vinyl radical to an alkene and giving the β -hydroxyethyl radical, which is oxidized to acetaldehyde by $\text{Mn}(\text{III})$.

1.1.4.3 Scope and Limitations

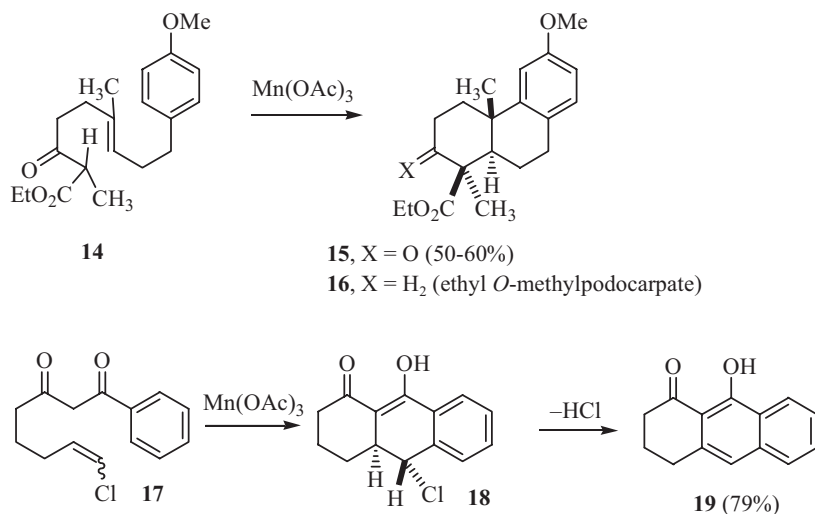
Cyclizations that form a single carbon–carbon bond can be accomplished by oxidative cyclization of unsaturated β -diketones, β -keto esters, or β -keto amides **11** that lead to cycloalkanones, unsaturated β -diketones, β -keto esters, or malonate esters **12** that lead to cycloalkanes, and unsaturated esters, or amides **13** that lead to lactams or lactones (Scheme 3) [5, 6].



Scheme 3. Substrates for oxidative cyclization.

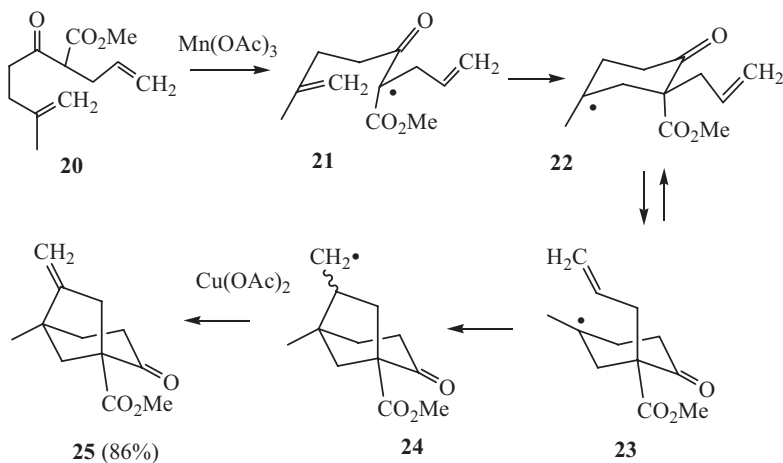
More complex targets can be made with excellent stereocontrol by tandem oxidative cyclizations. These reactions can be divided into two classes depending on whether the second cyclization is to an aromatic ring or to another double bond. Oxidative cyclization of **14** with 2 equiv. of $\text{Mn}(\text{OAc})_3$ in MeOH at 0°C provides 50–60% of **15** as a single stereoisomer. The structure of **15** was established by Clemmensen reduction to give ethyl *O*-methylpodocarpate (**16**), as shown in Scheme 4 [23–25]. Tandem cyclizations can also be terminated by cyclization to an arene conjugated with a carbonyl group. Oxidative cyclization of either the *E* or *Z* isomer of **17** with $\text{Mn}(\text{OAc})_3$ in acetic acid affords **18**, which undergoes slow loss of hydrogen chloride to afford 79% of the desired naphthol **19** [26–28]. Similar cyclizations were used for the first syntheses of okicenone and aloesaponol III.

The utility of tandem oxidative cyclizations is clearly demonstrated in substrates in which both additions are to double bonds [12]. Oxidative cyclization of **20** with two equivalents of $\text{Mn}(\text{OAc})_3$ and of $\text{Cu}(\text{OAc})_2$ in acetic acid at 25°C affords 86% bicyclo[3.2.1]octane **25**. Oxidation affords the α -keto radical **21**, which cyclizes exclusively 6-endo in the conformation shown to afford the tertiary radical **22** with



Scheme 4. Oxidative cyclization of **14** and **17**.

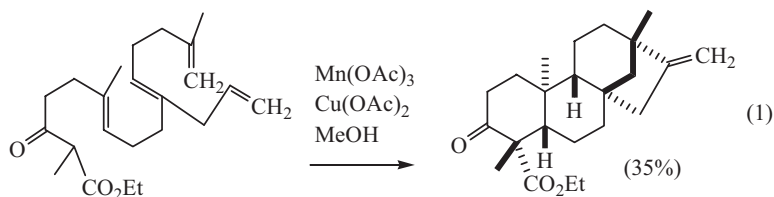
an equatorial allyl group. Chair–chair interconversion provides **23** with an axial allyl group. 5-exo-Cyclization of the 5-hexenyl radical of **23** gives **24** as a 2:1 mixture of exo and endo stereoisomers. Oxidation of both stereoisomers of **24** with Cu(II) provides **25**, as shown in Scheme 5.



Scheme 5. Oxidative cyclization of **20**.

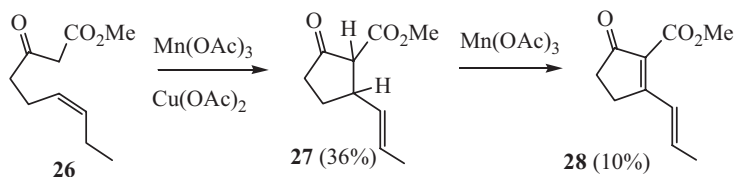
A wide variety of tandem, triple [12], and even quadruple [13, 14] cyclizations can be performed with multiply unsaturated 1,3-dicarbonyl compounds as shown in Eq. (1) [14]; this provides intermediates for steroid and terpene syntheses. High levels of asymmetric induction can be achieved with phenylmenthyl acetoacetate

esters and dimethylpyrrolidine acetoacetamides [25]. Recent results indicate that addition of $\text{Yb}(\text{Otf})_3$ in trifluoroethanol results in improved asymmetric induction [21]. The application of Mn(III)-mediated radical reactions to natural product total synthesis provides an excellent demonstration of the scope and utility of these reactions because the procedure is versatile enough to deal with complex skeletons and diverse functionality.



1.1.4.4 Common Side Reactions

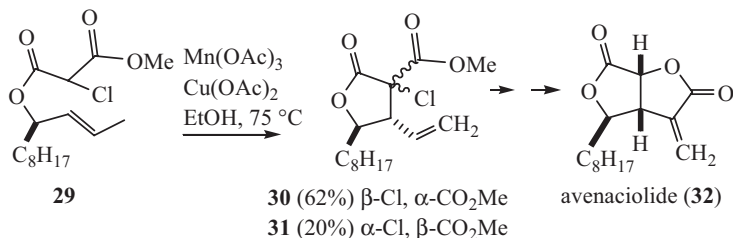
Oxidative cyclization of unsaturated β -dicarbonyl compounds with two α -hydrogen atoms will give products that still have one α -hydrogen and can be oxidized further. If the product is oxidized at a rate competitive with that of the starting material, mixtures of products will be obtained. For instance, oxidative cyclization of **26** affords 36 % of **27** and 10 % of dienone **28** formed by further oxidation of **27**, as shown in Scheme 6 [7]. The product is occasionally oxidized much more readily than the starting material so that none of the initial product is isolated. These reactions may still be synthetically useful if the products of further oxidation are monomeric. For example, oxidative cyclization of methyl 3-oxo-6-heptenoate provides 78 % of methyl salicylate [29]. The overall reaction consumes 4 equiv. $\text{Mn}(\text{OAc})_3$. Competitive oxidation of the product is not usually a problem in intermolecular addition reactions, because a vast excess of the oxidizable substrate, for example acetone or acetic acid, is usually used as solvent. Use of excess substrate is not possible in oxidative cyclizations.



Scheme 6. Oxidative cyclization of **26** and further oxidation of **27**.

Further oxidation cannot occur if there are no acidic α -hydrogens in the product. α -Chloro substituents serve as protecting groups preventing further oxidation of the product [30–33]. For instance, oxidative cyclization of **29** affords 82 % of a 3.1:1 mixture of **30** and **31**, as shown in Scheme 7 [31]. The other two stereoisomers with the octyl and vinyl groups *cis* are not formed. This mixture was elabo-

rated to avenaciolide (**32**) by a sequence that used an S_N2 reaction on the α -chloro lactone to form the second lactone ring.



Scheme 7. Synthesis of avenaciolide (**32**).

Experimental

Methyl 5-Methyl-6-methylene-2-oxobicyclo[3.2.1]octane-1-carboxylate (**25**)

To a stirred solution of $\text{Mn(OAc)}_3 \cdot 2\text{H}_2\text{O}$ (0.804 g, 3 mmol) and $\text{Cu(OAc)}_2 \cdot \text{H}_2\text{O}$ (0.300 g, 1.5 mmol) in 13.5 mL of glacial AcOH was added ketoester **20** (0.307 g, 1.5 mmol) in 4 mL of glacial AcOH. The reaction mixture was stirred at 25 °C for 26 h at which time the dark brown solution had turned light blue. Water (100 mL) was added and a 10 % NaHSO_3 solution was added to reduce any residual Mn(III). The resulting solution was extracted with CH_2Cl_2 ($3 \times 30\text{-mL}$). The combined organic layers were washed with saturated NaHCO_3 solution and dried over Na_2SO_4 . Concentration afforded 0.30 g (96 %) of a yellow solid that was recrystallized from pentane to give pure **25** (686 mg, 86 %): m.p. 71.8–72.5 °C; ^1H NMR (CDCl_3 , 300 MHz): δ = 5.08 (dd, J = 2.3, 3.1 Hz, 1H, =CH₂), 5.01 (dd, J = 2.3, 3.1 Hz, 1H, =CH₂), 3.76 (s, 3H, OMe), 2.94 (dddd, J = 0.9, 1.9, 3.1, 18.4 Hz, 1H, 7endo-H), 2.83 (br d, J = 18.4 Hz, 7exo-H), 2.52 (dddd, J = 1.0, 8.9, 12.5, 17.0 Hz, 1H, 3endo-H), 2.36 (ddd, J = 2.0, 6.9, 17.0 Hz, 1H, 3exo-H), 2.09 (br s, 2H, 8-H), 1.79 (ddd, J = 6.9, 12.0, 12.5 Hz, 1H, 4exo-H), 1.68 (dddd, J = 2.0, 2.0, 2.0, 8.9, 12.0 Hz, 1H, 4endo-H), 1.25 (s, 3H, 5-Me); ^{13}C NMR (CDCl_3 , 75 MHz) 207.5 (C2), 171.7 (CO₂), 153.5 (C6), 106.3 (=CH₂), 62.2 (C1), 52.1 (OMe), 47.0 (C8), 44.0 (C5), 40.3 (C4), 39.9 (C7), 35.5 (C3), 22.7 (C5-Me). Anal. Calcd for $\text{C}_{12}\text{H}_{16}\text{O}_3$: C, 69.21; H, 7.24; Found: C, 68.89; H, 7.88.

1.1.5

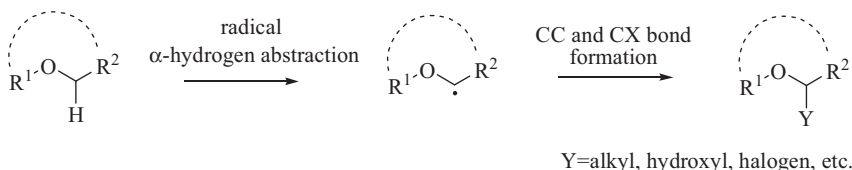
Radical α -Functionalization of Ethers

Takehiko Yoshimitsu

1.1.5.1 Introduction and Fundamental Examples

The susceptibility to hydrogen abstraction of C–H bonds α to ethereal oxygen, which often reflects thermochemical, polar, and stereoelectronic effects, enables selective functionalization of ethereal α -C–H bonds [1, 2]. The resulting α -alkoxyalkyl radicals stabilized by conjugative electron delocalization between the oxygen

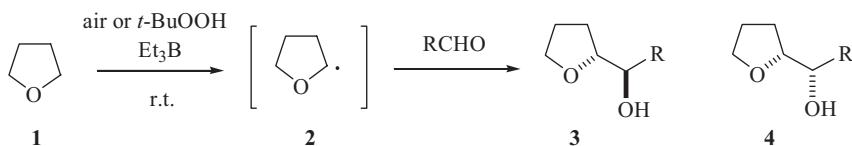
atom and the SOMO of the carbon-centered radical are nucleophilic and useful for synthetically important transformations of ethers. This type of C–H transformation involves carbon–carbon (C–C) and carbon–heteroatom (C–X) bond formation, as exemplified by alkylation [3], oxygenation [4], and halogenation [5] (Scheme 1).



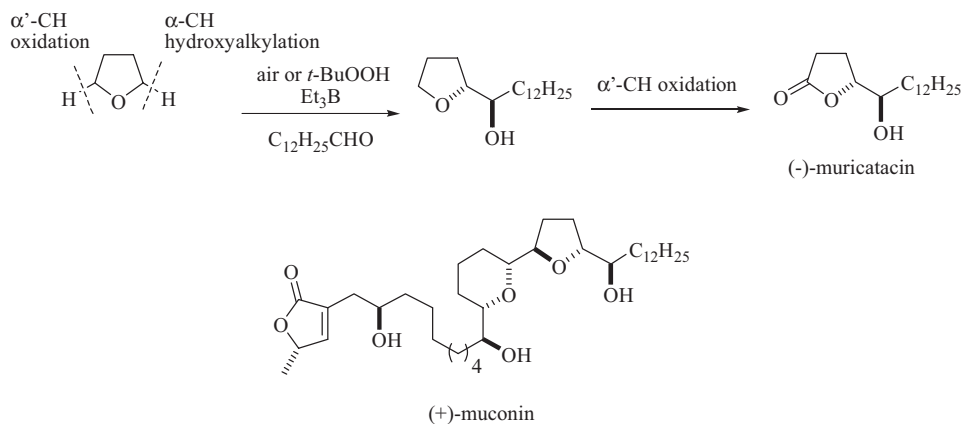
Scheme 1. Direct formation of C–C and C–X bonds via radical α -C–H transformation of ethers.

The radical C–H transformation of ethers is generally initiated by α -hydrogen abstraction with highly reactive radicals generated from such initiators as peroxides [3a, g], photo-activated carbonyl compounds [3b–d], metallic reagents [3i, j], and redox systems [3f, h]. Various combinations of ethers, radical initiators, and radical acceptors (e.g. carbon–carbon multiple bonds) may be used as the reaction components [6]. Several notable means of direct C–C bond formation via the radical α -C–H transformation of ethers involve the use of triflon derivatives [7], the phthalimide-*N*-oxyl (PINO) radical [8], 2-chloroethylsulfonyle oxime ethers [9], and *N*-acyl aldohydrazones [10].

One novel aspect of this chemistry has recently emerged, namely, the direct assembly of ethers with aldehydes [11, 12] and aldimines [13]. The α -C–H hydroxyalkylation of common ethers such as tetrahydrofuran (THF) with aldehydes using triethylborane–air [11,14] or triethylborane-*tert*-butyl hydroperoxide (TBHP) [12] as the radical initiator has been found to proceed efficiently (Scheme 2). This ethereal C–H transformation is of particular interest because the intermolecular coupling of carbon-centered radicals with aldehydes has hitherto met with limited success [15]. The present mode of C–H transformation of THF enables the unprecedented chemical transformation of the common cyclic ether into a γ -(hydroxyalkyl)- γ -butyrolactone that serves as a bioactive compound and as a useful building block in organic synthesis [16, 17]. For example, (–)-muricatacin, a potent cytotoxic (4*R*,5*R*)-5-hydroxyheptadecan-4-olide, was successfully synthesized via a sequence of α -C–H hydroxyalkylation and α' -C–H oxidation of THF (Scheme 3). The synthesis clearly shows that the direct transformation of ethereal α -C–H bonds to C–C and C–X bonds leads to greater flexibility in the synthetic design of oxygenated molecular frameworks.



Scheme 2. Radical α -C–H hydroxyalkylation of tetrahydrofuran with aldehydes [11, 12].



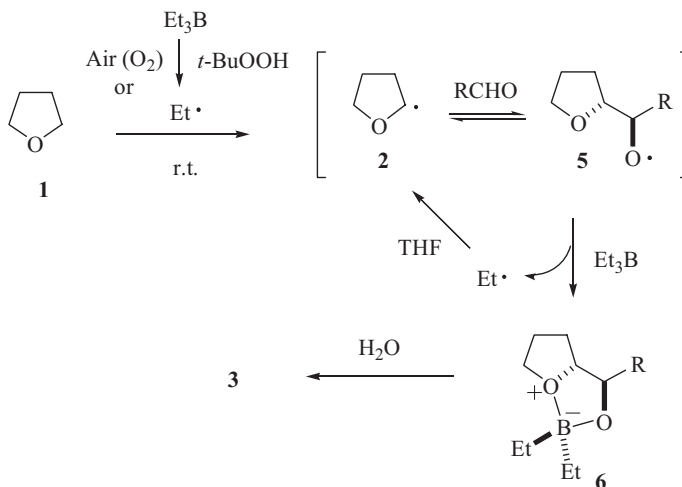
Scheme 3. Synthesis of bioactive natural products via α - and α' -C–H transformation of tetrahydrofuran [16, 17].

Several other ethers besides THF have been found to undergo the ethereal C–H transformation [18]. In the later part of this section the compatibility of this novel chemistry with various types of ethers and a related compound will be described. Similar reactions resulting in direct assembly of ethers with aldimines using dimethylzinc–air as the radical initiator also have a significant potential for developing this new field of chemistry [13]. Because of space limitations, however, the author will focus on the novel α -C–H hydroxyalkylation of ethers with aldehydes.

1.1.5.2 Mechanism

One plausible mechanism of the α -C–H hydroxyalkylation of THF, a representative ether substrate, is shown in Scheme 4. After abstraction of the α -hydrogen of THF with an ethyl radical generated from triethylborane–air or TBHP [19], the resulting nucleophilic THF radical **2** reacts with aldehydes to provide alkoxy radicals **5**. Alkoxy radical intermediates **5** are captured by triethylborane, although possible complexation of Lewis acidic triethylborane with the aldehydes before oxyradical generation may be involved. Because **5** have been shown to be highly unstable, owing to their inherently high reactivity and the thermochemical strength of the C=O bonds of the starting aldehydes [12], reversion of **5** to **2** in Scheme 4 is favored unless **5** are immediately captured by triethylborane. The oxophilic and Lewis acidic properties of triethylborane are thought to be responsible for the successful transformation, because dimethylzinc, a weak Lewis acid, has been shown to be a superior promoter of α -aminoalkylation but to be less potent in this α -C–H hydroxyalkylation [13b, c]. These experiments suggest that triethylborane plays the roles both of a radical initiator and of an oxyradical scavenger. The same mechanistic consideration can be applied to the triethylborane–TBHP system in which ethyl radical generation occurs more rapidly via facile decomposition of triethylborane with TBHP. It is also worth mentioning that aldehydic

hydrogen, often susceptible to homolytic rupture, is tolerant, probably because of the slow rate of the hydrogen abstraction by a nucleophilic ethyl radical.



Scheme 4. Plausible mechanism of α -C–H hydroxyalkylation of tetrahydrofuran (1) mediated by Et₃B–air or Et₃B–TBHP.

1.1.5.3 Scope and Limitations

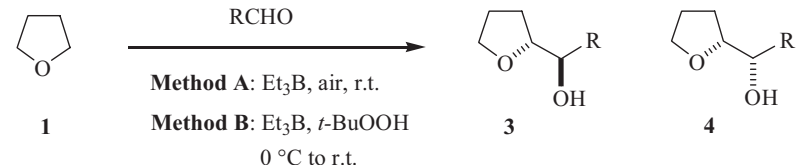
1.1.5.3.1 Structural diversity of aldehydes:[11,12]

The α -C–H hydroxyalkylation of THF (1) with aldehydes provides α -alkylated products in comparable yields under triethylborane–air (method A) or triethylborane–TBHP (method B) conditions (Table 1). The ease of operation and the relatively mild conditions are the merits of the former, whereas a short reaction time makes the latter highly efficient. Table 1 shows the general applicability of the two methods to various aldehydes. The yield and threo selectivity of products 3:4 are generally high for all aromatic aldehydes except ortho-substituted benzaldehyde (entry 4) and moderate to low for aliphatic substrates (entries 5 and 6).

1.1.5.3.2 Structural Diversity of Ethers and Related Compounds [18]

Table 2 shows that in addition to THF (1), ethers and an acetal such as diethyl ether (7), oxetane (9), 2-methyltetrahydrofuran (12) and 1,3-dioxolane (11) undergo α -C–H hydroxyalkylation to provide adducts in good yields. Dibutyl ether (8) (64 % yield; dr 71:29) and oxepane (10) (63 % yield; dr 88:12) have also been found to afford α -hydroxyalkylated ethers under the same conditions in moderate yields [20]. It is interesting to note that the reaction selectively provides threo alcohols (entries 1–5). Occasionally, ethyl adducts and/or 4-methoxybenzylalcohol are produced, but the amounts of the byproducts are usually negligible.

Table 1. α -C–H hydroxyalkylation of tetrahydrofuran with aldehydes under Et_3B –air or Et_3B –TBHP conditions.

					
Entry	Aldehyde	Method ^a	Reaction time	Yield (%) ^b	3 : 4 ^c
1	4-MeOC ₆ H ₄ CHO a	A	13 h	83	89 : 11
		B	5 min	80	90 : 10
2	PhCHO b	A	11 h	76	86 : 14
		B	5 min	82	86 : 14
3	piperonal c	A	8 h	80	88 : 12
		B	5 min	79	89 : 11
4	2-BrC ₆ H ₄ CHO d	A	5 h	82	71 : 29
		B	5 min	78	69 : 31
5	C ₁₂ H ₂₅ CHO e	A	11 h	61	64 : 36 ^f
		B	70 min	65 ^{d,e}	64 : 36 ^f
6	C ₆ H ₁₁ CHO f	B	70 min	43 ^{d,e}	45 : 55 ^f

^a Method A: the reaction was carried out with a slight modification of the original protocol [11]; ca. 120 equiv. THF, 6 equiv. Et_3B with continuous admission of air (ca. 30 mL h^{-1} mmol aldehyde⁻¹). Method B: the reaction was carried out using 106 equiv. THF, 10 equiv. Et_3B and 6 equiv. TBHP. Ref. [12].

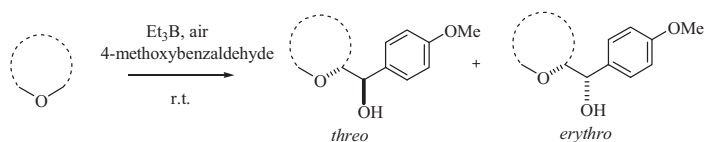
^b Isolated yields based on aldehydes.


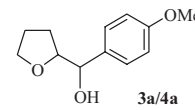

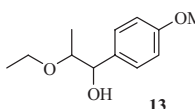
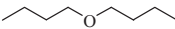
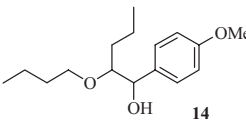

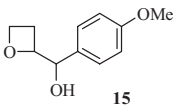

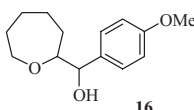

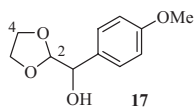

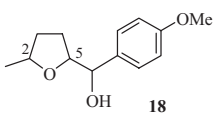
^c Ratios determined by ^1H NMR of *threo*/*erythro* mixture.

^d Two-step yields of diastereomeric acetates from **3/4**.

^e Isolated yield based on recovered aldehyde.

^f Ratios determined by ^1H NMR of acetates.

Table 2. α -C–H hydroxyalkylation of ethers and acetal with 4-methoxybenzaldehyde under Et_3B –air conditions [18].

Entry	Ether	Product	Concn, ^a time ^b	Yield (%) ^c	Diastereomeric ratio (<i>threo</i> : <i>erythro</i>)
1	 1	 3a/4a	100 mM 13 h	83	89:11 ^d
2	 7	 13	50 mM 22 h	72 ^f	74:26 ^d
3	 8	 14	30 mM 20 h	64 ^g	71:29 ^d
4	 9	 15	130 mM 15 h	77	78:22 ^e
5	 10	 16	75 mM ^h 20 h	63	88:12 ^e
6	 11	 17	120 mM 9 h	79 ⁱ	–
7	 12	 18	100 mM 12 h	84 ^j	–

^a Aldehyde concentration in ethers or an acetal; all reactions except entry 5 were carried out using 6 equiv. Et_3B (relative to aldehyde).

^b Air was introduced at a rate of ca. 30 mL h^{−1} mmol aldehyde^{−1}.

^c Isolated yields based on aldehyde.

^d Ratio determined by ¹H NMR measurement of *threo*/*erythro* mixture.

^e Ratio determined based on separated isomers.

^f 1-(4-Methoxyphenyl)propan-1-ol (3%) and 4-methoxybenzyl alcohol (6%) were also produced.

^g Unreacted aldehyde (7%) was recovered.

^h 10 equiv. Et_3B was used.

ⁱ Combined yield of regioisomeric C2/C4 hydroxyalkylation products (C2:C4=68:11).

^j Combined yield of regioisomeric C5/C2 hydroxyalkylation products (C5:C2=54:46). The stereochemistry of the adducts has yet to be determined.

It should be emphasized that the flow rate of air strongly influences the reaction rate – the reaction is substantially accelerated by greater admission of air to the reaction mixture (e.g. ca. 30 mL h⁻¹ mmol aldehyde⁻¹ for 13 h compared with ca. 20 mL h⁻¹ mmol aldehyde⁻¹ for 33 h for completion of the α -hydroxyalkylation of THF with 4-methoxybenzaldehyde).

Although careful consideration must be given to all the factors influencing the efficiency of α -hydrogen abstraction of ethers, oxyradical capture, and substrate tolerance, one may devise reactive hydrogen abstractors such as the methyl radical [13] that would broaden the applicability of the ethereal C–H transformation. For example, in the α -aminoalkylation of ethers using dimethylzinc–air, a wide range of ethers and related compounds have been shown to be compatible with the C–H transformation [13a, d]. The wide applicability reflects the efficient α -hydrogen abstraction with a highly reactive methyl radical with large exothermicity for the abstraction step. Because the intermolecular coupling of ether radicals with aldehydes is rarely recognized as strategic means for C–C bond formation in organic synthesis, the radical C–H transformation of ethers presented in this chapter is expected to be of considerable interest to synthetic practitioners and will provide a basis for new C–H transformation chemistry.

Experimental

Representative Procedure for the α -Hydroxyalkylation of THF with Aldehydes using Triethylborane and Air (Method A)

To 4-methoxybenzaldehyde (408 mg, 3.0 mmol) in THF (30 mL, 370 mmol) was added Et₃B (2.6 mL, 18 mmol) at room temperature under an argon atmosphere. (*Caution: Triethylborane, a liquid pyrophoric toward oxygen, should be handled to avoid exposure to air.*) After removal of the Ar balloon, the mixture was stirred at the same temperature with continuous bubbling of air through a syringe needle with a balloon (flow rate; ca. 30 mL h⁻¹ mmol aldehyde⁻¹) for 13 h. The reaction mixture was treated with 28 % NH₄OH and extracted with CH₂Cl₂. (NH₄OH solution (28 %) and CH₂Cl₂ used in combination enable removal of an unidentified polar byproduct that may have originated in Et₃B. Removal, from the crude mixture, of the polar by-product, which is detectable on an iodine–silica gel TLC plate, may otherwise be difficult. The crude mixture must be washed with 28 % NH₄OH solution for adequate purification.) The organic extract was dried over MgSO₄. After solvent evaporation in vacuo, the residue was purified by silica gel column chromatography (AcOEt–Hex 1:2) to give a colorless solid consisting of alcohols **3a/4a** (520 mg, 83 %) as a diastereomeric mixture (dr 89:11).

threo- α -(4-Methoxyphenyl)tetrahydro-2-furanmethanol (**3a**): colorless solid, m.p. 50–52 °C; IR (neat) ν_{\max} 3437 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.29 (d, 2H, *J* = 8.8 Hz), 6.88 (d, 2H, *J* = 8.8 Hz), 4.39 (d, 1H, *J* = 6.84 Hz), 3.98 (dd, 1H, *J* = 14.4, 7.08 Hz), 3.94–3.82 (m, 2H), 3.80 (s, 3H), 2.95 (s, 1H), 1.98–1.80 (m, 2H), 1.75–1.65 (m, 1H), 1.64–1.53 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 159.2, 132.7,

128.1, 113.7, 83.5, 76.6, 68.4, 55.3, 27.9, 26.1; MS (EI) m/z : 208 (M^+), 190, 137 (100 %); HRMS calcd for $C_{12}H_{16}O_3$ (M^+) 208.1100, found 208.1100.

erythro- α -(4-Methoxyphenyl)tetrahydro-2-furanmethanol (**4a**): colorless solid, m.p. 72–74 °C; IR (neat) ν_{\max} 3427 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.28 (d, 2H, $J=8.8$ Hz), 6.87 (d, 2H, $J=8.8$ Hz), 4.84 (m, 1H), 4.06–4.01 (m, 1H), 3.93–3.87 (m, 1H), 3.81–3.75 (m, 1H), 3.79 (s, 3H), 2.56 (s, 1H), 1.88–1.76 (m, 3H), 1.67–1.62 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 158.8, 132.7, 127.1, 113.6, 83.1, 73.8, 68.9, 55.2, 26.0, 25.1; MS (EI) m/z : 208 (M^+), 190, 137 (100 %); HRMS calcd for $C_{12}H_{16}O_3$ (M^+) 208.1100, found 208.1102.

General Procedure for the α -Hydroxyalkylation of THF with Aldehydes using Triethylborane (1.0 M in THF) and TBHP (Method B) [12]

To aldehydes (1.0 mmol) was added 1.0 M Et_3B in THF (10 mL, 10 mmol) at 0 °C under an argon atmosphere. After 15 min, 5.78 M *t*-butyl hydroperoxide (TBHP) in nonane (1.0 mL, 6.0 mmol) was added dropwise to the mixture at the same temperature. After being stirred for 10 min, the mixture was left to warm to room temperature and stirred for an additional period during which the reaction proceeded to completion. The reaction mixture was treated with 28 % NH_4OH and extracted with CH_2Cl_2 . The organic extract was dried over MgSO_4 . After solvent evaporation *in vacuo*, the residue was purified by silica gel column chromatography to give alcohols **3/4** (AcOEt–hexane as eluent).

Using a Modification of Method B: [15] *threo*- α -Dodecyltetrahydrofurfuryl Alcohol (**3e**)/*erythro*- α -Dodecyltetrahydrofurfuryl alcohol (**4e**)

To a solution of tridecanal (2.0 g, 10.0 mmol) in THF (57 mL, 700 mmol) at 0 °C was added Et_3B (8.7 mL, 5.88 g, 60.0 mmol) under an argon atmosphere. After 8 min of stirring, 6.24 M *tert*-butyl hydroperoxide in nonane (12.8 mL, 80.0 mmol) was added dropwise to the reaction mixture over a period of 30 min. (**Caution:** Addition of peroxides to triethylborane may lead to a highly exothermic reaction. We encountered no violent reaction with these procedures but special care is advised.) After being stirred at room temperature for 1 h, the reaction mixture was left to cool to 0 °C and treated with 28 % NH_4OH and then sat. $\text{Na}_2\text{S}_2\text{O}_3$. The mixture was extracted with Et_2O and washed with brine. The organic extract was dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (AcOEt–hexane 1:4) to give alcohols **3e/4e** (1.47 g, 64 % based on tridecanal; 0.3 g recovery) as a colorless oil. The diastereomeric ratio was determined by ^1H NMR analysis of acetates derived from alcohols **3e/4e**.

threo- α -Dodecyltetrahydro-2-furanmethanol (**3e**): colorless waxy solid; IR (neat) ν_{\max} 3470 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 3.80–3.63 (m, 3H), 3.38–3.30 (m, 1H), 2.59 (brs, 1H), 1.85–1.82 (m, 3H), 1.60–1.15 (m, 23H), 0.83 (t, 3H, $J=6.6$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 82.4, 73.8, 67.9, 33.7, 31.9, 29.7, 29.63, 29.62, 29.60, 29.58, 29.56, 29.3, 27.9, 26.2, 25.7, 22.6, 14.0; MS (EI) m/z : 270 (M^+), 252, 71 (100 %); HRMS calcd for $C_{17}H_{34}O_2$ (M^+) 270.2550, found 270.2554.

erythro- α -Dodecyltetrahydro-2-furanmethanol (**4e**): colorless waxy solid; IR (neat) ν_{\max} 3449 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 3.90–3.84 (m, 1H), 3.80–

3.72 (m, 3H), 2.09 (brs, 1H), 1.92–1.74 (m, 4H), 1.55–1.20 (m, 23H), 0.87 (t, 3H, $J = 6.8$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 82.2, 71.9, 68.5, 32.9, 32.0, 29.8, 29.7, 29.69, 29.65, 29.61, 29.4, 26.2, 26.0, 24.5, 22.7, 14.2; MS (EI) m/z : 270 (M^+), 252, 71 (100 %); HRMS calcd for $\text{C}_{17}\text{H}_{34}\text{O}_2$ (M^+) 270.2550, found 270.2559.

1.1.6

Aerobic Oxidation of Alcohols

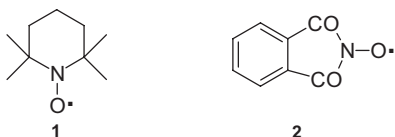
Francesco Minisci and Ombretta Porta

1.1.6.1 Introduction

The oxidation of alcohols to the corresponding aldehydes, ketones and carboxylic acids is one of the most important C–H transformations in organic chemistry, for both general synthetic purposes and industrial applications (see section 1.1.7 for enantioselective oxidations of alcohols). A large variety of oxidants have been used for these oxidations, including metal salts (of Cr, Mn, and Ru), Swern oxidation by activated $\text{SO}(\text{CH}_3)_2$, Dess–Martin periodinane, and related reagents [1, 2]. These oxidations, still widely used, are not convenient economically or environmentally. Modern ecological standards require the development of new catalytic processes characterized not only by oxidant-economy, but also by environmental benignity (i.e. involving clean oxidants such as hydrogen peroxide [3, 4] or molecular oxygen). In particular, O_2 is a very convenient and potent oxidant, but its direct use is restricted by spin conservation because of its triplet ground state structure, thus, catalysis is necessary for aerobic oxidation of alcohols under mild conditions. Both homogeneous and heterogeneous catalysis have been widely used and recent reviews are available [5].

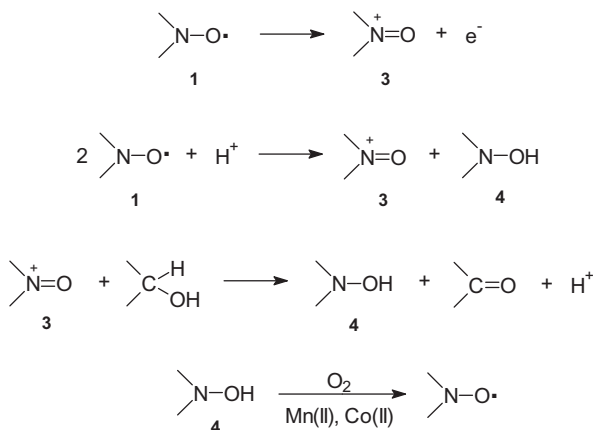
1.1.6.2 Mechanism

The mechanism of the aerobic oxidation of alcohols depends on the particular catalyst used. Two general mechanisms can be considered: (1) the direct oxygenation of alcohols by O_2 through a free-radical chain process initiated by the catalyst, and (2) the direct oxidation of the alcohol by the catalyst, which is then regenerated by O_2 . Both mechanisms are well illustrated [6] by the aerobic oxidations catalyzed by the persistent tetramethylpiperidine-*N*-oxyl (TEMPO) radical **1** and the nonpersistent phthalimide-*N*-oxyl (PINO) radical **2**.



The fundamental difference between the two catalysts is related to the bond-dissociation enthalpies of the O–H bonds of the corresponding *N*-hydroxy derivatives [6]. Whereas **1** is an inhibitor of free radical chains, **2** induces free-radical chains

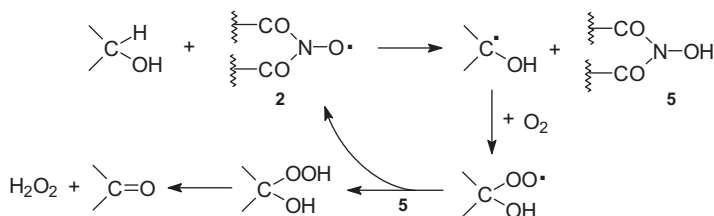
because hydrogen abstraction from alcohols is largely endothermic with **1** and thermoneutral or slightly exothermic with **2**. The mechanism of oxidation catalyzed by **1** involves formation of the oxoammonium salt **3** by either oxidation or acidic disproportionation of **1**; the actual oxidant of the alcohol is **3**, while the role of O_2 associated to metal salts is the regeneration of **1** and **3** from the hydroxylamine derivative **4** (Scheme 1).



Scheme 1. Mechanism of alcohol oxidation catalyzed by TEMPO.

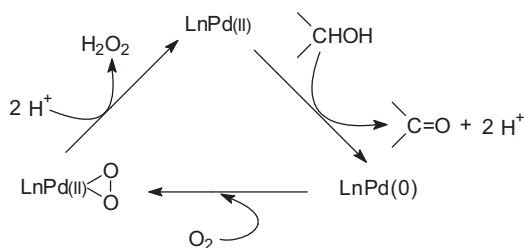
The mechanism of the oxidation, catalyzed by **2**, involves a free-radical chain in which the rate-determining step is hydrogen abstraction from C–H by **2** (Scheme 2).

A free-radical mechanism is also operating in the aerobic oxidation of alcohols, catalyzed by metalloprotein galactose oxidase, in which the rate determining step is hydrogen abstraction from the alcohol by the coordinated tyrosyl radical [7]. A different mechanism was suggested for the aerobic oxidation of alcohols catalyzed by $\text{Ru}(\text{PPh}_3)_3\text{Cl}_2/\text{TEMPO}$ – the alcohol would be dehydrogenated by the Ru complex with formation of a Ru hydride ($\text{RuH}_2(\text{PPh}_3)_3$) and the carbonyl compound. Whereas the Ru hydride would generate a complex catalytic cycle with TEMPO and the alcohol, O_2 would regenerate TEMPO from the *N*-hydroxytetramethylpiperidine [5d].



Scheme 2. Mechanism of alcohol oxidation catalyzed by PINO.

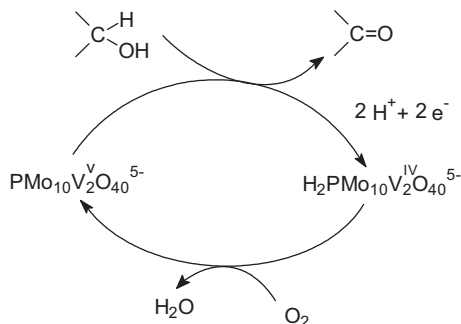
Pd(II) complexes have also been used for aerobic oxidation of alcohols to the corresponding carbonyl compounds – the mechanism likely involves the reduction of Pd(II) to Pd(0) by the alcohol. In this reaction also the role of O_2 is the regeneration of Pd(II) through a Pd–peroxo intermediate [8] (Scheme 3).



Scheme 3. Mechanism of alcohol oxidation catalyzed by Pd(II) complexes.

It has been suggested that the mechanism of the heterogeneous aerobic oxidation of alcohols catalyzed by Pt, Pd, and other noble metals proceeds via an oxidative dehydrogenation in which the alcohols are adsorbed and dehydrogenated on the metal surfaces and the adsorbed hydrogen is then oxidized to water by O_2 . Another interpretation assumes that the rate-determining step involves direct interaction of the adsorbed oxidizing species with the adsorbed reactant or its partially dehydrogenated intermediate. According to another, different, mechanism, the primary role of O_2 is the oxidative cleaning of the surface sites, suppressing catalyst deactivation, and not the oxidation of the coproduct hydrogen [5c].

The aerobic oxidation of alcohols by heteropolyoxometalates has been interpreted [5b, c] according to the Scheme 4.



Scheme 4. Mechanism of alcohol oxidation catalyzed by heteropolyoxometalates.

1.1.6.3 Scope, Limitations and Fundamental Examples

The nitroxyl-based systems are the most important and widely investigated homogeneous catalysts for the aerobic and non-aerobic oxidation of alcohols [9]. The different mechanisms with persistent (Scheme 1) and nonpersistent (Scheme 2) nitroxyl radicals is reflected in the selectivity of primary alcohol oxidation. Several

metal salt complexes have been used, in combination with TEMPO-based systems, for the aerobic oxidation of alcohols [5]. Among these, the bimetallic Mn(II)–Co(II) or Mn(II)–Cu(II) nitrates seem to be the most convenient and effective [5a, 6, 10].

TEMPO has a double role – it generates the oxoammonium salt, responsible for the oxidation (Scheme 1), and inhibits the further oxidation of aldehydes and ketones, which occurs instead via free-radical chain processes under the same conditions, but in the absence of TEMPO [5a]. Thus, this catalytic system is highly effective for one of the most demanding transformations, the selective synthesis of aldehydes from benzylic and nonbenzylic alcohols.

With nonpersistent nitroxyl radicals (PINO, Scheme 2) benzyl alcohols give, selectively, the aromatic aldehydes, whereas aliphatic alcohols lead to the carboxylic acids [12], even at low conversions [6]. This behavior has been explained on the basis of the prevailing polar effect [6, 13] in the abstraction of hydrogen from benzyl alcohols and by the dominant enthalpic effect in the abstraction of hydrogen from aliphatic alcohols [6].

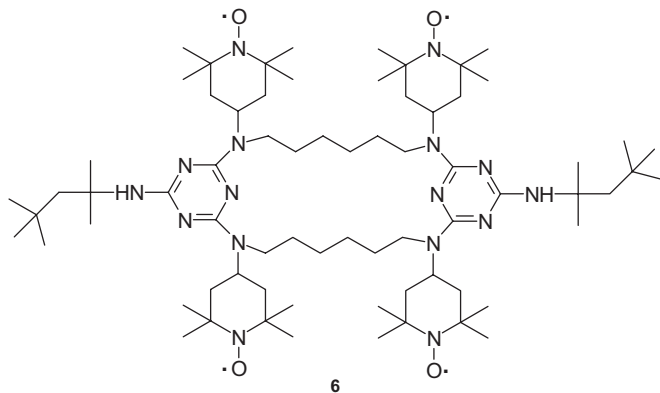
Catalysis by TEMPO has the advantage of being general for oxidation of both benzylic or non benzylic alcohols to aldehydes, whereas catalysis by PINO, although limited to the synthesis of aromatic aldehydes, has the advantage that the radical is generated in situ from the less expensive *N*-hydroxyphthalimide, which can be more easily recovered and recycled.

The advantages of heterogeneous catalysis over homogeneous are easier product isolation and recycling of the catalysts after separation. The development of supported TEMPOs could provide a solution to re-use the expensive catalyst. Nowadays, several supported catalysts have been developed by anchoring TEMPO to solid supports, for example silica (mesoporous silica MCM-41), and by entrapping TEMPO in a sol-gel or using nitroxyl derivatives of oligomeric amines (Mw ca. 3000) [5].

Heterogeneous TEMPO catalysts have much lower catalytic efficiency than their homogeneous counterparts, however. A convenient compromise [4, 5a, 6] is the use of the nitroxyl radical **6**, prepared from the commercially available antioxidant Chimassorb 966. This catalyst, which is soluble in acidic medium, is quite effective in promoting the aerobic oxidation under mild conditions and, after easy recovery, can be conveniently reused [4, 5a, 6].

Pd(II) catalysts have been widely used for aerobic oxidation of alcohols. The catalytic systems Pd(OAc)₂–(CH₃)₂SO [14] and Pd(OAc)₂–pyridine [15] oxidize allylic and benzylic alcohols to the corresponding aldehydes and ketones. Secondary aliphatic alcohols, with relatively high water solubility, have been oxidized to the corresponding ketones by air at high pressure, at 100 °C in water, by using a water-soluble bathophenanthroline disulfonate palladium complex [PhenS*Pd(OAc)₂] [5d]. The Pd catalyst has also been successfully used for aerobic oxidative kinetic resolution of secondary alcohols, using (–)-sparteine [16].

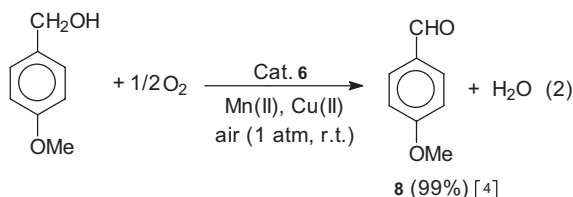
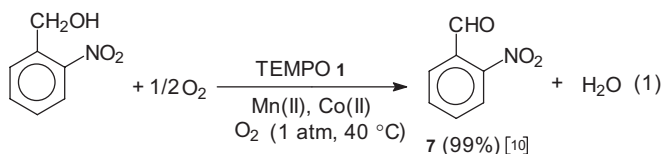
Aerobic oxidation of alcohols to the corresponding aldehydes, ketones, and carboxylic acids can be performed in aqueous solution by using noble metals as catalysts under mild conditions, but severe deactivation of the catalysts often occurs, seriously limiting process development [5b, c, e].

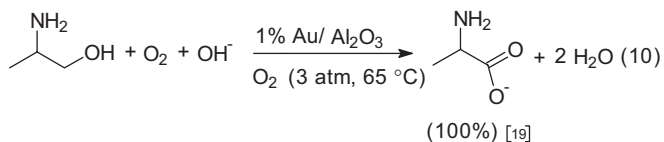
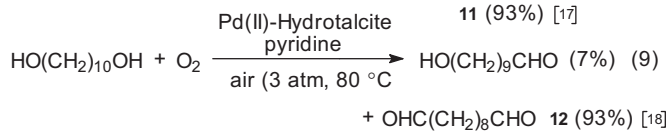
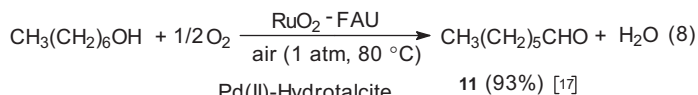
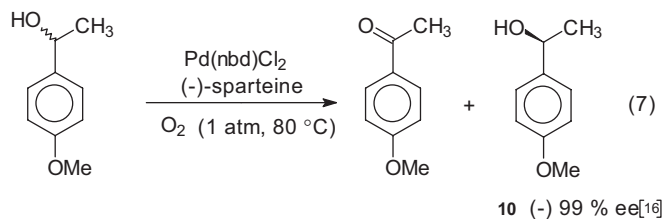
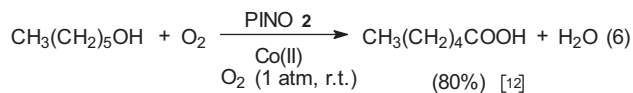
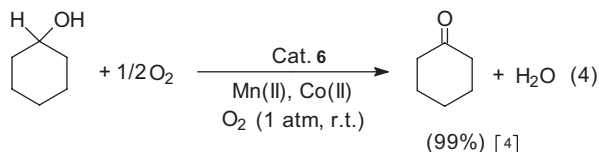
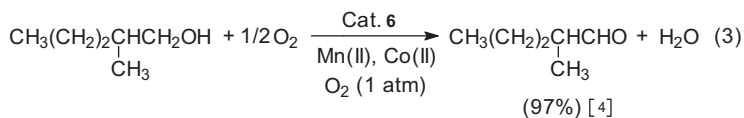


A variety of supported metal complexes (i.e. Pd(II), Ru(III), polyoxametalates, perruthenates) have also been used as catalysts in the aerobic oxidation of alcohols [5b, c], even if, in general, the catalytic activity is lower than for homogeneous catalysis, emphasizing the increasing interest for this particularly important C–H transformation. Nanometer-sized RuO_2 clusters in supercages of faujasite zeolite ($\text{RuO}_2\text{-FAU}$) are active catalysts of the aerobic oxidation of alcohols [17]. Pd(II)-hydrotalcite efficiently catalyzes the aerobic oxidation of benzyl alcohol to benzaldehyde in the presence of pyridine as a cocatalyst [18].

In all the reactions discussed above metal salt complexes are always fundamental catalysts or cocatalysts of the aerobic oxidation. Aerobic oxidation has recently been performed, in the absence of metal salts, by using $\text{HNO}_3 + \text{Br}_2$ in a two-phase system ($\text{H}_2\text{O}/\text{ClCH}_2\text{CH}_2\text{Cl}$) as a catalyst [19]. Primary benzyl alcohols selectively give the corresponding aldehydes whereas aliphatic alcohols lead to the esters (Eqs. 13 and 14) via a free radical process in which the actual oxidant, Br_2 , is continuously regenerated from HBr by O_2 through HNO_3 and nitrogen oxides.

Representative examples are illustrated by Eqs. (1)–(14).







A solution of 92.6 mmol (12.8 g) 4-methoxybenzyl alcohol, 2.25 mmol nitroxyl radical **6**, 4.5 mmol *p*-toluensulfonic acid, 1.8 mmol $\text{Mn}(\text{NO}_3)_2$, and 1.8 mmol $\text{Cu}(\text{NO}_3)_2$ in 100 mL CH_3COOH was stirred at r.t. for 3 h under air at atmospheric pressure. The CH_3COOH was then evaporated at ca. 55 torr and the reaction product was extracted with methyl-*t*-butyl ether (the salt of the nitroxyl radical **6** with *p*-toluensulfonic acid, can be recovered and recycled). GC analysis (4-methylbenz-

aldehyde as internal standard) revealed 4-methoxybenzaldehyde in 99 % yield. Flash column chromatography on silica gel yielded 12.1 g pure 4-methoxybenzaldehyde (b.p. 248 °C; 96 % yield). The nitroxyl catalyst **6**, in the form of the *p*-toluensulfonic acid salt, has been recycled four times without significant loss of activity.

Synthesis of 3-Cyanobenzaldehyde (9) by Aerobic Oxidation of 3-Cyanobenzyl Alcohol, Catalyzed by *N*-Hydroxyphthalimide [11]

A solution of 3 mmol 3-cyanobenzyl alcohol, 0.3 mmol *N*-hydroxyphthalimide, 0.015 mmol Co(OAc)₂, and 0.15 mmol *m*-chlorobenzoic acid in 15 mL acetonitrile was stirred at r.t. for 4 h under O₂ at atmospheric pressure. GC analysis (3-chlorobenzaldehyde as internal standard) revealed 3-cyanobenzaldehyde in 98 % yield. Flash column chromatography on silica gel yielded 2.8 mmol of pure 3-cyanobenzaldehyde (m.p. 77–78 °C; 93 % yield).

Aerobic Oxidative Kinetic Resolution of 1-(4-Methoxyphenyl)ethanol (10), Catalyzed by Pd(nbd)Cl₂ and (–)-sparteine [16]

An oven-dried reaction tube (o.d. 16 mm, length 120 mm) equipped with a magnetic stir bar was charged with oven dried powdered molecular sieves (MS 3 Å, 0.5 g). After cooling, Pd(nbd)Cl₂ complex (0.05 mmol) was added, followed by toluene (2 mL) and (–)-sparteine (0.2 mmol). The flask was cooled at –78 °C, then vacuum evacuated and filled with O₂ and heated at 60 °C for 15 min. Powdered Cs₂CO₃ (1 mmol), with a toluene solution (2 mL) of 1-(4-methoxyphenyl)ethanol (1 mmol) and *t*-BuOH (1.5 mmol), was introduced. The reaction mixture was kept at 80 °C for 13 h and, after cooling, the solution was filtered through a small plug of silica gel (Et₂O as eluent), evaporated and analyzed. Percent conversions were measured by GC integration of the 1-(4-methoxyphenyl)ethanol and 4-methoxyacetophenone peaks, correcting for the response factor. The enantiomeric excess was measured by chiral HPLC (Chiralcell OD-H, 4 % EtOH–hexane 1 mL min^{–1}, retention times 16.88 and 18.66 min for (R) and (S) isomers, respectively). Conversion 68 %; ee of (–)-1-(4-methoxyphenyl)ethanol 99 %.

Synthesis of Heptanal (11) by Aerobic Oxidation of 1-Heptanol, Catalyzed by RuO₂–FAU [17]

A mixture of 1 mmol 1-heptanol, 3 mL toluene, and 0.1 g RuO₂–FAU catalyst was stirred at 80 °C for 20 h under ambient pressure of air. The oxidation product was analyzed and quantified by GC with an internal standard and identified by GC–MS. GC analysis was performed on a Supelco MDN-55 column (30 m × 0.25 mm × 0.50 μm) with a Perkin–Elmer Auto System GC equipped with an FID. GC–MS was performed with a Perkin–Elmer Auto System XLGC with a Perkin–Elmer Turbo Mass spectrometer. Yield of heptanal was 93 %.

Synthesis of 1,10-Decanedialdehyde (12) by Aerobic Oxidation of Decane-1,10-diol, Catalyzed by Pd(II)–Hydrotalcite [18]

Pyridine (0.2 mol) was added to a suspension of Pd(II)-hydrotalcite (300 mg, 0.05 mmol as Pd) in 6 mL of toluene. The mixture was stirred at r.t., air was intro-

duced at atmospheric pressure and the mixture was heated at 65 °C for 10 min. Next, 1 mmol decane-1,10-diol in 4 mL of toluene was added and the mixture was vigorously stirred for 3 h at 80 °C under air at 3 atm. The catalyst was separated by filtration, and removal of the solvent under reduced pressure left on an oily residue which was subjected to flash column chromatography (hexane–diethyl ether as eluent) to give 0.73 mmol 1,10-decanedialdehyde as a colorless oil (^1H NMR δ 1.26–1.43 (m, 8 H), 1.60–1.65 (m, 4 H), 2.43 (td, J = 1.7, 7.3 Hz, 4 H), 9.76 (t, J = 1.7 Hz, 2H); ^{13}C NMR δ 22.0, 29.1, 29.1, 43.9, 202.9) and 0.05 mmol 10-hydroxydecanal (^1H NMR δ 1.26–1.43 (m, 11 H), 1.52–1.67 (m, 4 H), 2.42 (td, J = 1.6, 7.3 Hz, 2H), 3.62–3.66 (m, 2H), 9.76 (t, J = 1.6 Hz, 1H); ^{13}C NMR δ 22.1, 25.7, 29.2, 29.3, 29.3, 29.4, 32.8, 43.9, 63.1, 203.0).

1.1.7

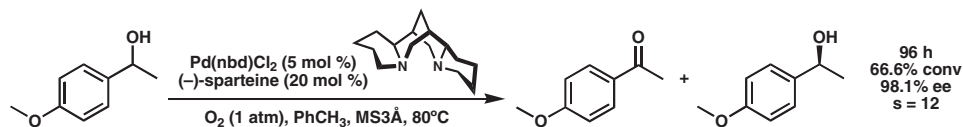
Kinetic Resolution by Enantioselective Aerobic Oxidation of Alcohols

Brian M. Stoltz and David C. Ebner

1.1.7.1 Introduction and Fundamental Examples

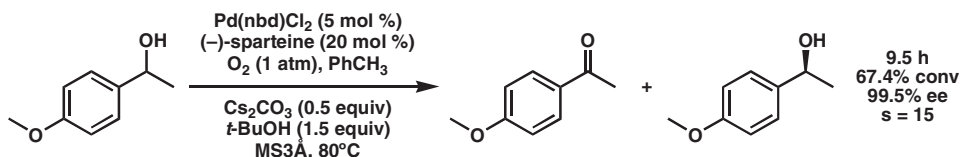
The oxidation of alcohols to aldehydes and ketones is one of the most common and well-studied reactions in organic chemistry [1]. Many of these processes require organic or metal oxidants. It is much more desirable to find systems that utilize oxygen and a catalyst to perform alcohol oxidation, because of the environmental and economic benefits. A number of important advances have been made in this area, as described in the preceding section (IV.1.1.6). Recently, several groups have developed enantioselective aerobic alcohol oxidations, enabling kinetic resolution of secondary alcohols [2].

In 1998, Uemura reported the aerobic oxidation of alcohols in the presence of $\text{Pd}(\text{OAc})_2$ and pyridine in the noncoordinating solvent toluene [3]. No reaction was observed when pyridine was absent. Recognizing the effect of pyridine as a rate-accelerating ligand, the Stoltz [4] and Sigman [5] groups simultaneously reported nearly identical systems for oxidative kinetic resolution of secondary alcohols using a modification of the Uemura system employing (–)-sparteine as a chiral ligand (Scheme 1). A key observation made by Stoltz was the large counterion effect present in the reaction, and chloride was found to be optimum for high reactivity and selectivity. This asymmetric oxidation could be applied as a kinetic resolution of secondary alcohols or as a desymmetrization of meso diols. Furthermore, the product ketone in the reaction could be trivially reduced to racemic alcohol and resolved again.



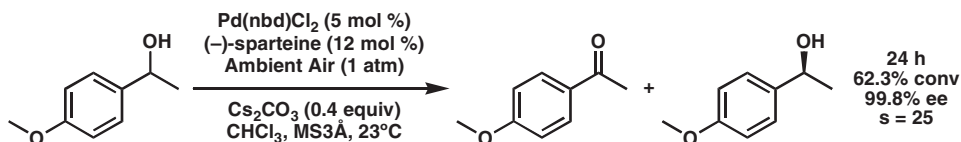
Scheme 1. Original Pd(II)-catalyzed aerobic kinetic resolution conditions [4].

Although this system was useful for preparation of optically enriched secondary alcohols, prolonged reaction times limited the practicality of the process. Stoltz found that addition of Cs_2CO_3 and *t*-BuOH dramatically increased the reaction rate, leading to more practical reaction timescales while maintaining selectivity (Scheme 2) [6].



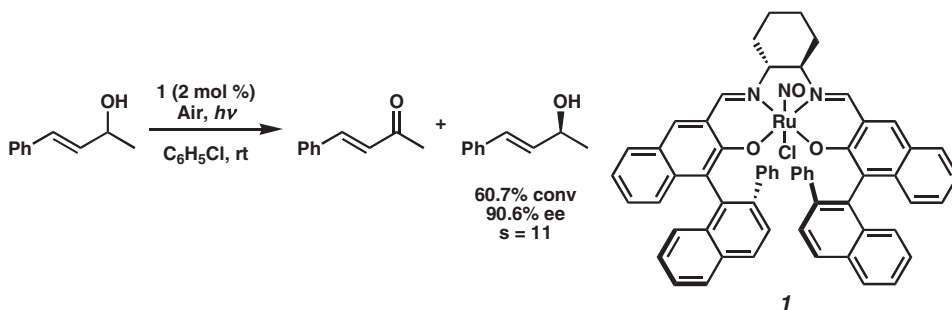
Scheme 2. Improved Cs_2CO_3 /*t*-BuOH conditions [6].

The role of *t*-BuOH as an accelerant in this reaction was not obvious, and Sigman had subsequently shown that *t*-BuOH was a suitable solvent for oxidation of a range of substrates, even for some nonactivated secondary alcohols [7]. These results prompted Stoltz to further investigate the effect of solvent on this reaction. It was found that CHCl_3 was uniquely effective as a solvent for these alcohol oxidations [8]. Resolution in CHCl_3 was highly selective with a range of secondary alcohols. Furthermore, the solvent change enabled these resolutions to be performed at 23 °C and using ambient air instead of pure oxygen (Scheme 3).



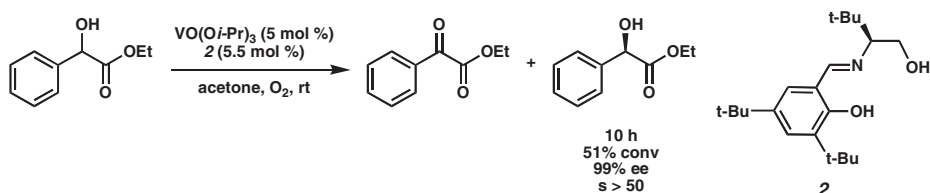
Scheme 3. CHCl_3 conditions for enantioselective alcohol oxidation [8].

Several other systems have been discovered for the aerobic oxidative kinetic resolution of secondary alcohols. Katsuki has shown that (nitroso)Ru-salen complexes such as **1** can successfully resolve alcohols under photolytic conditions in the presence of dry air (Scheme 4) [9]. A related Ru complex was also able to achieve



Scheme 4. Kinetic resolution with (nitroso)Ru-salen complex **1** [9].

desymmetrizations of primary meso diols [10]. Very recently, Toste has demonstrated the aerobic kinetic resolution of a variety of α -hydroxycarbonyl compounds in the presence of $\text{VO}(\text{O}i\text{-Pr})_3$ and imine **2** (Scheme 5) [11]. Surprisingly, although both catalysts are very similar to epoxidation systems, neither results in significant olefin oxidation under the reported conditions.

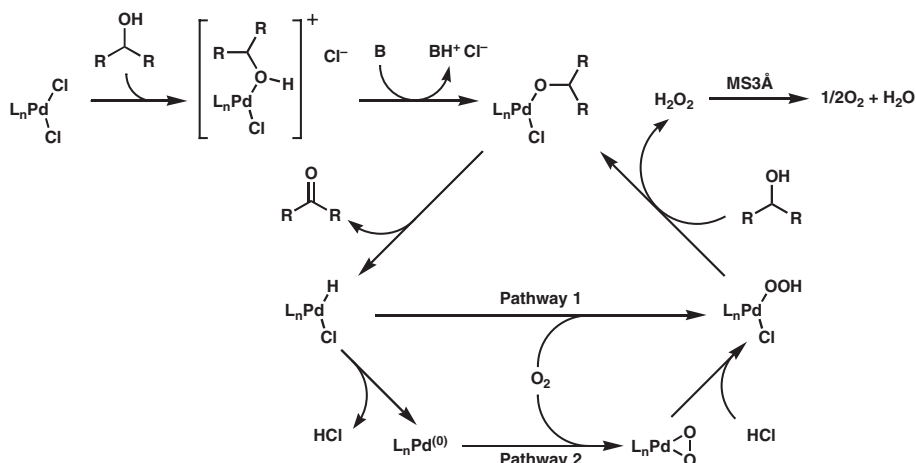


Scheme 5. Vanadium-catalyzed kinetic resolution of hydroxycarbonyls [11].

1.1.7.2 Mechanism

Mechanism has been most thoroughly studied in the $\text{Pd}(\text{II})$ system. Under these conditions, oxidation presumably begins with substitution of an alcohol for a chloride followed by alcohol deprotonation, resulting in a palladium alkoxide complex (Scheme 6) [12]. β -Hydride elimination then leads to a $\text{Pd}\text{--H}$ complex. Kinetic analyses by Stahl [13] and Sigman [14] confirm that the rate-limiting step in the reaction is β -hydride elimination. Interestingly, Sigman found that at low (–)-sparteine concentration, deprotonation of the $\text{Pd}(\text{II})$ –alcohol complex is rate-limiting [15]. This data corroborates the observation that excess amine relative to palladium is necessary for the reaction to proceed. An exogenous base, for example Cs_2CO_3 , enables lower sparteine loading, as seen in the conditions with CHCl_3 as solvent [8].

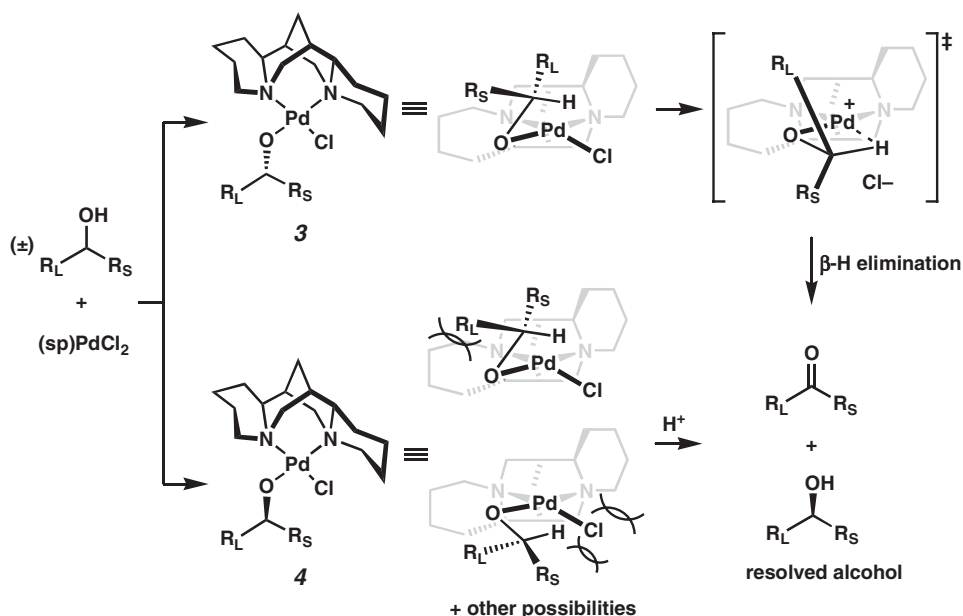
Two alternative pathways for catalyst turnover after β -hydride elimination have been proposed. Uemura proposed direct insertion of O_2 into $\text{Pd}\text{--H}$ (Pathway 1)



Scheme 6. Mechanism of alcohol oxidation by $\text{Pd}(\text{II})$.

[3]. Stahl, however, has shown that Pd(0), in the presence of a bulky bathocuproine (bc) ligand, reacts with dioxygen to form a peroxo derivative [16]. Treatment of the peroxo-Pd complex with acetic acid forms (bc)Pd(OAc)₂, suggesting the intermediacy of similar Pd(0) and peroxo-Pd(II) complexes in the catalytic cycle (Pathway 2). The catalyst turnover remains an unresolved issue for the (–)-sparteine-Pd(II) system.

X-ray crystallographic work by Stoltz [17] and calculations by Stoltz and Goddard [18] have provided some understanding of the origin of selectivity in the enantioselective aerobic oxidation by Pd(II) (Scheme 7). Complex 3, corresponding to the faster-reacting alcohol enantiomer, is believed to undergo facile β -hydride elimination. Complex 4, formed with the slower-reacting alcohol enantiomer, experiences unfavorable steric interactions in the transition state leading to β -hydride elimination, and eventually the alkoxide is protonated and dissociates from the Pd complex.



Scheme 7. Model of origin of stereoselectivity in Pd(II)-catalyzed kinetic resolution [17, 18].

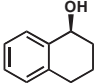
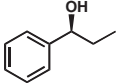
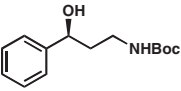
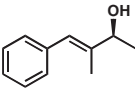
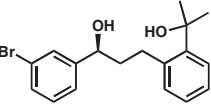

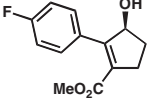
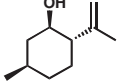
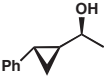

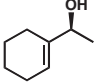

Mechanistic work on the aforementioned ruthenium and vanadium systems has been more limited. Katsuki has proposed a possible mechanism for the (nitroso)Ru-salen catalyzed oxidation. Photolytic dissociation of NO enables coordination of alcohol. Presumably, O₂ then performs two sequential one-electron oxidations to yield the ketone and hydrogen peroxide. This sequence is based primarily on the performance of certain alcohols in the oxidation [10].

Mechanistic evidence for vanadium(V)-catalyzed alcohol oxidation is even more limited. Preliminary work suggests vanadium(IV) is present in the reaction; however, a radical mechanism is not believed to be operating [11].

1.1.7.3 Scope and Limitations

Examination of the scope of the individual kinetic resolution systems leads to some general trends. Typically, oxidation proceeds most rapidly with activated alcohols, for example benzylic, allylic, and α -cyclopropyl alcohols. Occasionally, saturated alkyl alcohols can be oxidized, although reaction times are usually longer. Furthermore, sterically encumbered alcohols tend to be difficult to oxidize. Selectivity in the kinetic resolutions presumably relies on steric differences between the two alcohol substituents.

Table 1. Pd(II)-catalyzed kinetic resolution substrate scope.

$\text{R}-\text{CH}(\text{OH})-\text{R}' \xrightarrow[\text{(-)-sparteine}]{\text{Pd(II)}} \text{R}-\text{C}(=\text{O})-\text{R}' + \text{R}-\text{CH}(\text{OH})-\text{R}'$									
Entry	Alcohol	Conditions ^[a]	s ^[b]	Ref.	Entry	Alcohol	Conditions	s	Ref.
1		A	16	4	7		D	22	8
2		A	18	19	8		D	16	8
3		B	15	19	9		E	16	7
4		B	51	19	10		E	14	7
5		C	28	20	11		E	20	7
6		C	13	20	12		E	17	7

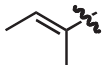
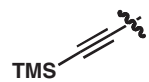
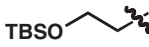
^a Kinetic resolution conditions A: 5 mol% Pd(nbd)Cl₂, 20 mol% (–)-sparteine, MS 3 Å, O₂ (1 atm), 0.1 M in PhCH₃, 80 °C. Conditions B: 5 mol% Pd(nbd)Cl₂, 20 mol% (–)-sparteine, 0.5 equiv. Cs₂CO₃, 1.5 equiv. *t*-BuOH, MS 3 Å, O₂ (1 atm), 0.25 M in PhCH₃, 60 °C. Conditions C: 5 mol% Pd(nbd)Cl₂, 12 mol% (–)-sparteine, 0.4 equiv. Cs₂CO₃, MS 3 Å, O₂ (1 atm), 0.25 M in CHCl₃, rt. Conditions D: 5 mol% Pd(nbd)Cl₂, 12 mol% (–)-sparteine, 0.4 equiv. Cs₂CO₃, MS 3 Å, air (1 atm), 0.25 M in CHCl₃, rt. Conditions E: 5 mol% Pd(sparteine)Cl₂, 20 mol% (–)-sparteine, MS 3 Å, O₂, 0.25 M in *t*-BuOH, 65 °C, 20 h

^b The selectivity factor *s* was determined using the equation: $s = k_{\text{rel}}(\text{fast/slow}) = \ln [(1 - C)(1 - ee)] / \ln [(1 - C)(1 + ee)]$, where *C* = conversion and *ee* is enantiomeric excess of alcohol.

The scope of the Pd(II)-catalyzed enantioselective oxidation system has been the most extensively explored. The conditions are able to selectively oxidize a wide variety of benzylic alcohols with high selectivity (Table 1, entries 1–3, 7) [4, 6–8]. Electron-withdrawing groups on the aromatic ring lead to lower oxidation rates and selectivity. Other types of aromatics can also be resolved successfully (entry 9), although N-containing heterocycles have little reactivity. Allylic and cyclopropyl alcohols are also well tolerated in the resolution (entries 5, 6), occasionally with extraordinary levels of selectivity (entry 4) [19]. As already mentioned, Sigman has shown that use of *t*-BuOH as solvent can also lead to useful enantioselective oxidation for some saturated alkyl alcohols (entries 10–12).

Toste's vanadium oxidation system currently has more limited scope, although it seems to be orthogonal to the Pd(II) system. Whereas the Pd–sparteine system was unable to effectively resolve α -hydroxycarbonyl compounds, these alcohols were resolved with high selectivity using vanadium(V) (Table 2) [11]. Benzylic and allylic α -hydroxycarbonyls performed well in the reactions (entries 1–3, 6). Alkyl hydroxy esters were oxidized more slowly, but with high selectivity (entry 5). Activated alcohols not α to a carbonyl led to poor selectivity or low reactivity.

Table 2. Substrate scope for vanadium-catalyzed kinetic resolution of secondary alcohols [11].

$ \begin{array}{c} \text{OH} \\ \\ \text{R}_1\text{---CH---C(=O)R}_2 \end{array} \xrightarrow[\text{acetone, O}_2, \text{rt}]{\text{VO(Oi-Pr)}_3 \text{ (5 mol \%)} \\ \text{2 (5.5 mol \%)}} \begin{array}{c} \text{O} \\ \\ \text{R}_1\text{---C---C(=O)R}_2 \end{array} + \begin{array}{c} \text{OH} \\ \\ \text{R}_1\text{---CH---C(=O)R}_2 \end{array} $				
Entry	R ₁	R ₂	Time (h)	s
1	<i>p</i> -MeOPh–	OMe	5.5	13
2	<i>p</i> -CF ₃ Ph–	OMe	4.0	29
3		OBn	16	18
4		OEt	16	6
5		OMe	144	42
6	Ph–	NH ^t Bu	12	12

Very few alcohols have been reported for the (nitroso)Ru–salen system (Table 3) [10]. The system shows good selectivity toward related secondary allylic (entry 1), benzylic (entry 2), propargylic (entry 3), and saturated alkyl (entry 4) alcohols.

Table 3. Scope of Ru-catalyzed aerobic kinetic resolution [9].

$ \begin{array}{c} \text{OH} \\ \\ \text{R}-\text{CH}-\text{R}' \end{array} \xrightarrow[\text{solvent, rt}]{\begin{array}{c} \text{1 (2 mol \%)} \\ \text{Air, } h\nu \end{array}} \begin{array}{c} \text{O} \\ \\ \text{R}-\text{C}-\text{R}' \end{array} + \begin{array}{c} \text{OH} \\ \\ \text{R}-\text{CH}-\text{R}' \end{array} $			
Entry	Substrate	Solvent	s
1		C ₆ H ₅ Cl	11
2		C ₆ H ₅ Cl	11
3		C ₆ H ₅ Cl	20
4		C ₆ H ₅ CH ₃	11

Experimental

Pd(II) Kinetic Resolution Original Conditions: (–)- α -Methyl-2-naphthalenemethanol [4]

A 500-mL round-bottomed flask was charged with powdered 3-Å molecular sieves (14.5 g) and a magnetic stir-bar and flame-dried under vacuum. After cooling under dry N₂, Pd(nbd)Cl₂ (391 mg, 1.45 mmol, 0.05 equiv.) then toluene (290 mL) and (–)-sparteine (1.34 mL, 5.81 mmol, 0.20 equiv.) were added. The flask was evacuated under vacuum and purged with O₂ (3×), and the reaction mixture was heated to 80 °C with vigorous stirring under an O₂ atmosphere (balloon) for 10 min. α -Methyl-2-naphthalenemethanol (5.00 g, 29.0 mmol, 1.0 equiv.) was then added, and the reaction was left to proceed under an O₂ atmosphere at 80 °C. Aliquots were filtered through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed. Conversion was measured by GC. Enantiomeric excess was measured by chiral HPLC (Chiralcel OJ, 4 % *i*-PrOH/hexanes, 1.0 mL min^{–1} elution, retention times 38.7 and 31.3 min for the (R) and (S) isomers, respectively). After 112 h (55.0 % conversion), the reaction mixture was filtered through a small plug of silica gel (EtOAc eluent) and evaporated. Purification by column chromatography on silica gel (6:1 → 3:1 hexanes/EtOAc) provided 2-acetylnaphthalene (2.75 g, 55 % yield) and (–)- α -methyl-2-naphthalenemethanol (2.20 g, 44 % yield, 99.0 % ee) as white solids.

Pd(II) Kinetic Resolution Cs₂CO₃/*t*-BuOH Conditions: (–)- α -Methylbenzyl Alcohol [6]

To an oven dried reaction tube (outer diameter 16 mm, length 120 mm) with magnetic stir-bar were added oven dried powdered 3-Å molecular sieves (500 mg).

After cooling, Pd(nbd)Cl₂ (13.5 mg, 0.05 mmol), then toluene (2 mL), and then (–)-sparteine (46.9 mg, 46 μL, 0.20 mmol) were added. The reaction tube was cooled to –78 °C, then evacuated under vacuum and purged with O₂ (3×). The tube was heated (60 °C) with vigorous stirring under an O₂ atmosphere (balloon) for 20 min. Finely powdered Cs₂CO₃ (162.9 mg, 0.50 mmol) was added, followed by a solution of α-methylbenzyl alcohol (122.2 mg, 1.0 mmol) and *t*-BuOH (111.2 mg, 143 μL, 1.5 mmol) in toluene (2 mL). The reaction was left to proceed under an O₂ atmosphere (1 atm) at 60 °C. Aliquots were filtered through a small plug of silica gel (Et₂O eluent), evaporated, and analyzed. Conversion was measured by integration of alcohol and ketone GC peaks, correcting for response factor. Enantiomeric excess measured was measured by chiral HPLC (Chiralcel OD-H, 2 % EtOH/hexanes, 1.0 mL min^{–1} elution, retention times 19.7 and 29.0 min for (R) and (S) isomers, respectively). After 12.5 h (63.9 % conversion), the reaction mixture was filtered through a small plug of silica gel (Et₂O eluent) and evaporated. Purification by column chromatography on silica gel provided acetophenone and (–)-α-methylbenzyl alcohol (99.6 % ee).

Pd(II) Kinetic Resolution CHCl₃/O₂ Conditions: (–)-Methyl 2-(4-Fluorophenyl)-3-hydroxycyclopent-1-enecarboxylate [19]

To an oven-dried reaction tube with stir-bar were added oven dried powdered 3-Å molecular sieves (500 mg). After cooling, Pd(nbd)Cl₂ (13.5 mg, 0.05 mmol), then chloroform (2 mL, stabilized with amylenes), and then (–)-sparteine (28.1 mg, 27.6 μL, 0.12 mmol) were added. The reaction tube was cooled to –78 °C, then evacuated under vacuum and purged with O₂ (3×). The reaction was stirred vigorously at 23 °C under an O₂ atmosphere (balloon) for 15 min. Finely powdered Cs₂CO₃ (130.3 mg, 0.40 mmol) was added, then a solution of methyl 2-(4-fluorophenyl)-3-hydroxycyclopent-1-enecarboxylate (236.3 mg, 1.0 mmol) in chloroform (2 mL). The reaction was left to proceed under an O₂ atmosphere at 23 °C. Aliquots were filtered through a small plug of silica gel (Et₂O eluent), evaporated, and analyzed. Conversion was measured by GC integration of the alcohol peak relative to the internal standard (tridecane). Enantiomeric excess was determined by chiral HPLC (Chiralcel OB-H, 5 % EtOH/hexanes, 1.0 mL min^{–1} elution, retention times 22.3 and 18.2 min for the (R) and (S) enantiomers, respectively). After 9 h (50.8 % conversion), the reaction mixture was filtered through a plug of silica gel (Et₂O eluent), and concentrated. The residue was purified by column chromatography to yield methyl 2-(4-fluorophenyl)-3-oxocyclopent-1-enecarboxylate and (–)-methyl 2-(4-fluorophenyl)-3-hydroxycyclopent-1-enecarboxylate (94.7 % ee).

Pd(II) Kinetic Resolution CHCl₃/Air Conditions: (+)-(*E*)-3-Methyl-4-phenyl-3-buten-2-ol [8]

To an oven-dried reaction tube with stir-bar were added oven dried powdered 3-Å molecular sieves (500 mg). After cooling, Pd(nbd)Cl₂ (13.5 mg, 0.05 mmol), then chloroform (2 mL, stabilized with amylenes), and then (–)-sparteine (28.1 mg, 27.6 μL, 0.12 mmol) were added. The reaction tube was fitted with a short drying tube filled with Drierite (1.0×7.5-cm plug) and stirred vigorously at 23 °C for

15 min. Finely powdered Cs_2CO_3 (130.3 mg, 0.40 mmol) was added, followed by a solution of (*E*)-3-methyl-4-phenyl-3-buten-2-ol (162.2 mg, 1.0 mmol) in chloroform (2 mL). The reaction was left to proceed under a dry air atmosphere (1 atm) at 23 °C. Aliquots were filtered through a small plug of silica gel (Et_2O eluent), evaporated, and analyzed. Conversion was measured by integration of the alcohol and ketone GC peaks, correcting for response factor. Enantiomeric excess was measured by chiral HPLC (Chiralcel OD-H, 4 % *i*-PrOH/hexanes, 1.0 mL min⁻¹ elution, retention times 13.4 and 15.4 min for the (*R*) and (*S*) isomers, respectively). After 44 h (64.7 % conversion), the reaction mixture was filtered through a small plug of silica gel (Et_2O eluent) and evaporated. Purification by column chromatography on silica gel provided (*E*)-3-methyl-4-phenylbut-3-en-2-one and (+)-(*E*)-3-methyl-4-phenylbut-3-en-2-ol (98.9 % ee).

Pd(II) General Kinetic Resolution *t*-BuOH Conditions [7]

In a 100-mL two-necked round-bottomed flask fitted with a reflux condenser, 10 mmol of the racemic alcohol, 469 mg (2 mmol) (–)-sparteine, 205 mg (0.5 mmol) $\text{Pd}[(\text{–})\text{-sparteine}]\text{Cl}_2$, 1.0 g 3-Å molecular sieves, and 40 mL *t*-BuOH were combined. A balloon filled with oxygen gas was then attached to the top of the condenser via a three way joint. The apparatus was then evacuated (water aspirator) and refilled with oxygen from the balloon three times. The reaction mixture was then stirred magnetically while heating in an oil bath at 65 °C. Aliquots (0.1 mL) from the reaction were taken periodically via syringe, quenched with 2 % TFA/MeOH, and analyzed by GC or chiral HPLC. Conversions were measured relative to tetradecane internal standard or by ¹H NMR. After 24 h the mixture was cooled to room temperature, filtered through a pad of silica, washed with Et_2O , and concentrated under vacuum. Ketone product and optically active alcohol were then separated by column chromatography (5 % EtOAc/hexane → 15 % EtOAc/hexane).

V(V) General Kinetic Resolution Conditions [11]

To a 100-mL round-bottomed flask equipped with magnetic stir-bar was added 2 (110 mg, 0.33 mmol, 0.055 equiv.) then acetone (15 mL) at ambient temperature to form a yellow solution. $\text{VO}(\text{O}i\text{-Pr})_3$ (70 μL , 0.30 mmol, 0.05 equiv.) was then added, and the resulting dark solution was stirred under an atmosphere of oxygen for 15 min. The alcohol (6.0 mmol, 1.0 equiv.) was then added by means of a syringe as a solution in 15 mL of acetone with 50 mg inert internal standard (hexamethylbenzene or durene). Aliquots of the reaction mixture were removed by means of a syringe at intervals and filtered through silica gel (Et_2O eluent) to monitor for percentage conversion and enantiomeric excess. On completion of the reaction (~50 % conversion), silica gel was added to the reaction mixture to form a thick slurry, which was stirred for 30 min. The slurry was then filtered over a pad of silica gel (500 mL Et_2O eluent). The filtrate was concentrated on a rotary evaporator and the resulting residue was purified by column chromatography on silica gel.

Ru-salen Kinetic Resolution Conditions: (*R*)-4-Phenyl-3-butyn-2-ol [9]

To a solution of racemic 4-phenyl-3-butyn-2-ol (14.6 mg, 0.10 mmol) in chlorobenzene (1.0 mL) was added bicyclohexyl (16.6 mg, 0.10 mmol) as internal standard for GC analysis. An aliquot (50 μ L) of this solution was taken out of the flask as a zero point and passed through silica gel (8:2 hexane–EtOAc eluent) before analysis by GC. The Ru complex **1** (2.0 mg, 2.0 μ mol) was added to the remaining solution and the mixture was stirred in air at room temperature for 17 h with irradiation by fluorescent light (100 V, 25 W). To remove the complex the mixture was filtered through silica gel (8:2 hexane–EtOAc eluent) and analyzed by GC (65.3 % conversion). The filtrate was then concentrated and chromatographed on silica gel (8:2 hexane–EtOAc). Chiral HPLC analysis (Chiralcel OD-H, 15:1 hexane–*i*-PrOH) of the purified alcohol showed >99.5 % ee.

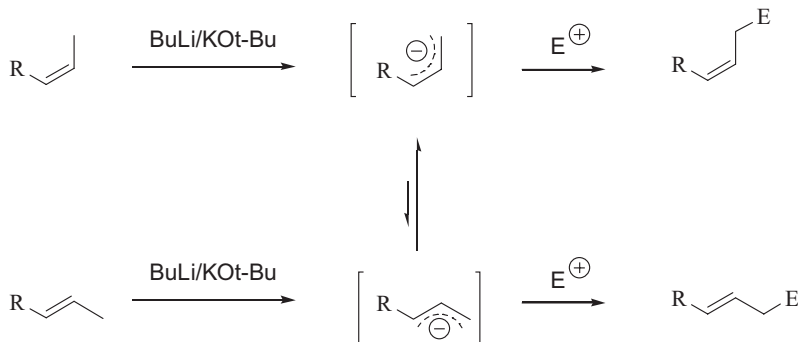
1.2**C–H Transformation in the Allylic and Benzylic Positions****1.2.1****C–H Transformation at Allylic Positions with the LICKOR Superbase**

A. Ganesan

1.2.1.1 Introduction and Fundamental Examples

Deprotonation of an allylic C–H bond in alkenes produces an allylic carbanion that is resonance stabilized. Thermodynamically, this suggests a favorable equilibrium when an alkene is reacted with Group 1 alkyllithium, alkylsodium, or alkylpotassium organometallics. The low kinetic reactivity of such reagents and their lack of regioselectivity (competing reactions are vinylic proton abstraction or addition to the alkene) hampered practical preparative transformations for many years, however. It was then discovered that alkyllithiums such as butyllithium or *t*-butyllithium are significantly activated by addition of *N,N,N',N'*-tetramethylenediamine (TMEDA) or potassium alkoxides. The 1:1 mixture of an alkyllithium (LiC) and a hindered potassium alkoxide (KOR, usually KO*t*-Bu), popularly known as “LICKOR” or “superbase” [1–3], is particularly efficient in the allylic deprotonation of linear and branched alkenes. With unsymmetrical alkenes, the LICKOR superbase is highly regioselective – allylic methyl groups are deprotonated much faster than methylenes, which in turn are much more reactive than methines. Like other allyl organometallics, the resulting carbanions are fluxional in character, and torsional equilibration interconverts the cisoid and transoid forms (Scheme 1). Allyllithium and allylmagnesium reagents undergo rapid isomerization without a strong preference for either geometrical isomer. On the other hand, allylpotassium species, which are likely to be involved in LICKOR deprotonations, are slow to isomerize. Because of the thermodynamic preference of larger Group 1 allylmetallic compounds (Na, K, Cs) to occur in the sterically more hindered *Z* form, the trapping of such species to give *Z* alkenes occurs with high stereochemical fidelity. At low temperatures, the *E* form obtained by deprotonating an *E*

alkene can be quenched with an electrophile, although some erosion of stereochemistry is often observed. These differences are also reflected in LICKOR deprotonation kinetics, Z alkenes reacting more rapidly than their E isomers. Thus, it is possible to start with a Z/E mixture of alkenes and selectively deprotonate the Z alkene. Alternatively, the mixture can be deliberately isomerized to the Z allyl species by equilibration at higher temperatures. The process is accelerated by the addition of transmetalation promoters such as pentene or solvents such as THF.

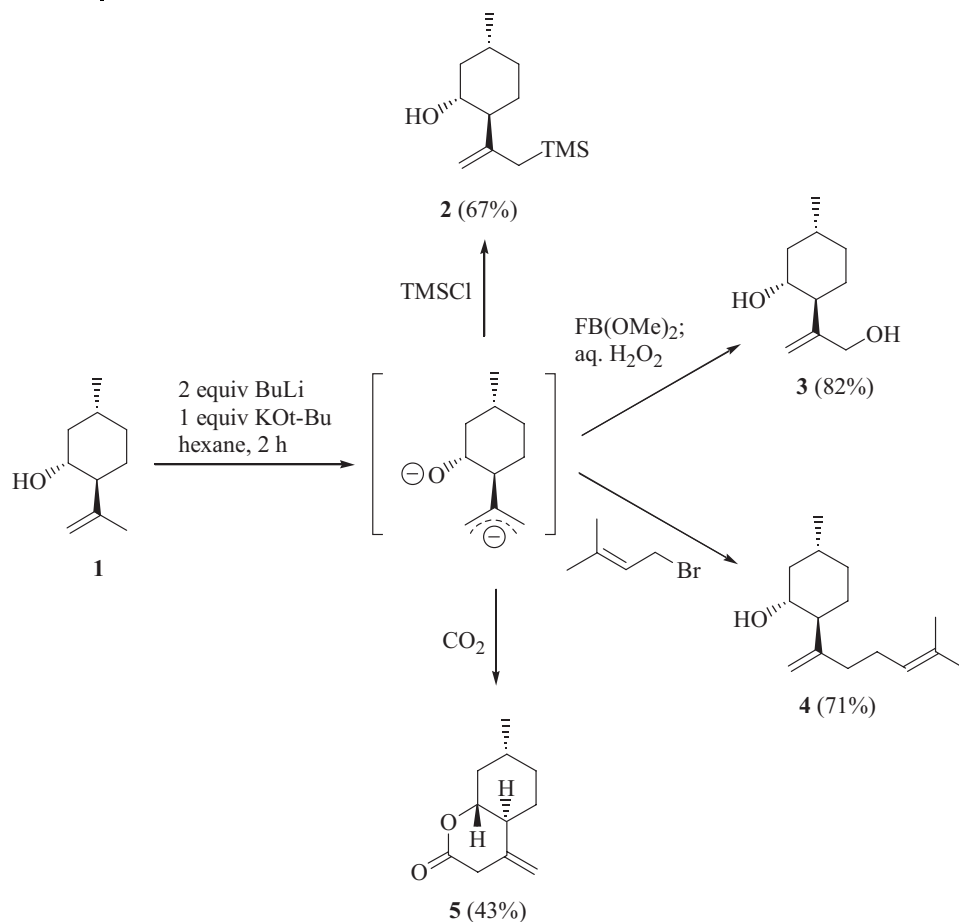


Scheme 1. The deprotonation of cis and trans olefins, followed by electrophilic trapping.

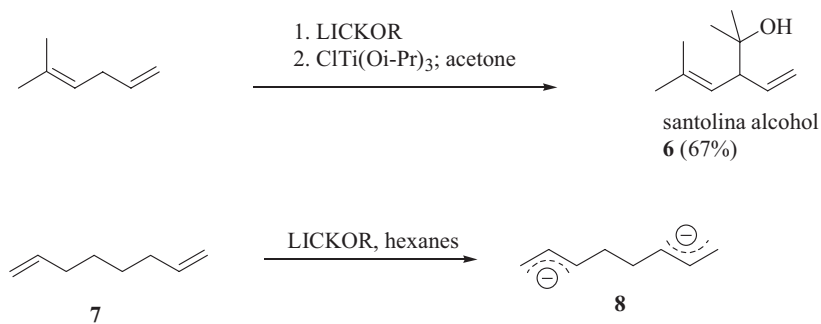
There are numerous examples of allylic deprotonations under LICKOR conditions, followed by trapping with a variety of electrophilic reagents. Among the more common electrophiles are: (1) trialkylsilyl chlorides, to give allylsilanes; (2) boron reagents, to give allylboronates or alcohols after oxidation with hydrogen peroxide; (3) alkyl halides and epoxides, to give homologated alkenes; (4) carbon dioxide, to give carboxylic acids; (5) aldehydes and ketones, to give homoallylic alcohols; and (6) transition metal salts, to give the transmetalated organometallic. Some of these possibilities are illustrated [4] with isopulegol **1** (Scheme 2). This example also shows that alcohols in the starting material do not need protection, being converted to the alkoxide with a second equivalent of base. With 1,3 or 1,4-dienes, the extended pentadienyl anion is formed (Scheme 3). An example is the short synthesis [5] of santolina alcohol **6**, which features transmetalation of the initial carbanion to an allyltitanium species. With systems containing two isolated alkenes, for example 1,7-octadiene, **7**, reaction with LICKOR yielded the dimetalated species **8** in hexanes, whereas monometalation was observed in THF [1]. Similar solvent dependence was obtained with 1,10-undecadiene, whereas with longer dienes such as 1,13-tetradecadiene the two alkenes were found to react independently in either solvent.

1.2.1.2 Mechanism

The alkylmetal–metal alkoxide combination was first described by Morton [6] for the anionic polymerization of butadiene – addition of an equivalent of sodium isopropoxide improved the catalytic activity of allylsodium. Fifteen years later the spe-



Scheme 2. LICKOR deprotonation of isopulegol, with representative trapping by electrophiles.



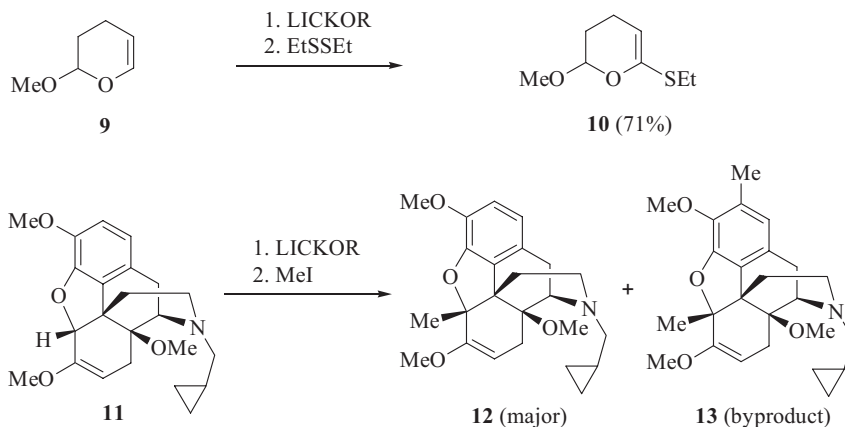
Scheme 3. LICKOR deprotonations of dienes.

cific LICKOR combination was reported [7] as a polymerization catalyst, and these “superbases” were further developed especially by the Schlosser [1] and Lochmann [2] groups. The true nature of the LICKOR reactive species, or the product of substrate deprotonation, remains unclear. When an alkyl lithium RLi and KO t -Bu are mixed in hexanes, metal interchange leads to RK, which precipitates, and LiOt-Bu, which can be removed by washing. Although generation of an alkylpotassium is clearly an important step in the LICKOR process, the reagent’s reactivity and selectivity profile seem to be different from that of an alkylpotassium alone. The structures of the BuLi–LiOt-Bu [8] and t -BuNLi–KO t -Bu–benzene [9] adducts have been solved by X-ray crystallography. The latter adduct, with superbase-like character, is a mixed-metal dimeric aggregate containing short Li–O bonds and benzene ligands coordinating to the potassium. It is probably best to view LICKOR as a similar mixed-metal aggregate with a weakened M–C bond resulting in high kinetic reactivity as a base. LICKOR substrates for deprotonation usually contain π -systems, and it is plausible that prior coordination to the potassium facilitates the process.

1.2.1.3 Scope and Limitations

Two general procedures are used to perform LICKOR deprotonations. Alkyl-lithium and potassium alkoxide can be combined to form the superbase before alkene addition, or the substrate mixed with one component of the superbase before addition of the other component. For LiC, n -BuLi, s -BuLi, and t -BuLi have all been used, whereas the hindered KOR component is most commonly KO t -Bu or sometimes potassium t -pentoxide. Although LICKOR generation is rapid even at low temperatures, substrate deprotonation can be sluggish. For this reason, an incubation period with the substrate at 0 °C or room temperature is often part of a LICKOR procedure. Such extended reaction times are also useful when torsional equilibration of the allylic carbanion is intended. Afterwards, the reaction mixture is cooled back to low temperature before addition of the electrophile. This is typically accompanied by a distinct color change from the vivid red of the allylic carbanion to yellow or decolorized reaction mixtures.

Given the nature of the LICKOR reagent, the substrate should not contain functional groups that are sensitive to main group organometallic compounds. Etheral solvents should be used at low temperature to avoid direct reaction with LICKOR, although acetals have been successfully used as alcohol-protecting groups in substrates. Besides deprotonation of allylic C–H bonds, LICKOR can react with benzylic and sp^2 alkene or arene C–H bonds. Reactions at such sites can be the major pathway, as seen in the deprotonation of enol ether **9** (Scheme 4) [10]. In the alkylation of the morphinan **11** by methyl iodide [11], the desired allylic addition product **12** was accompanied by **13**, in which additional alkylation occurred on the aromatic ring.




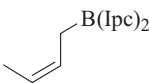

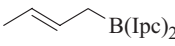
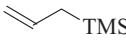
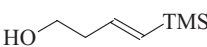
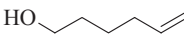
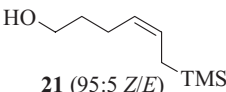
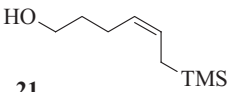
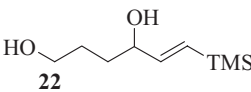


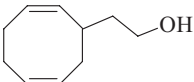

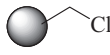
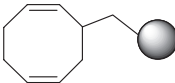
Scheme 4. Examples of non-allylic LICKOR deprotonations.

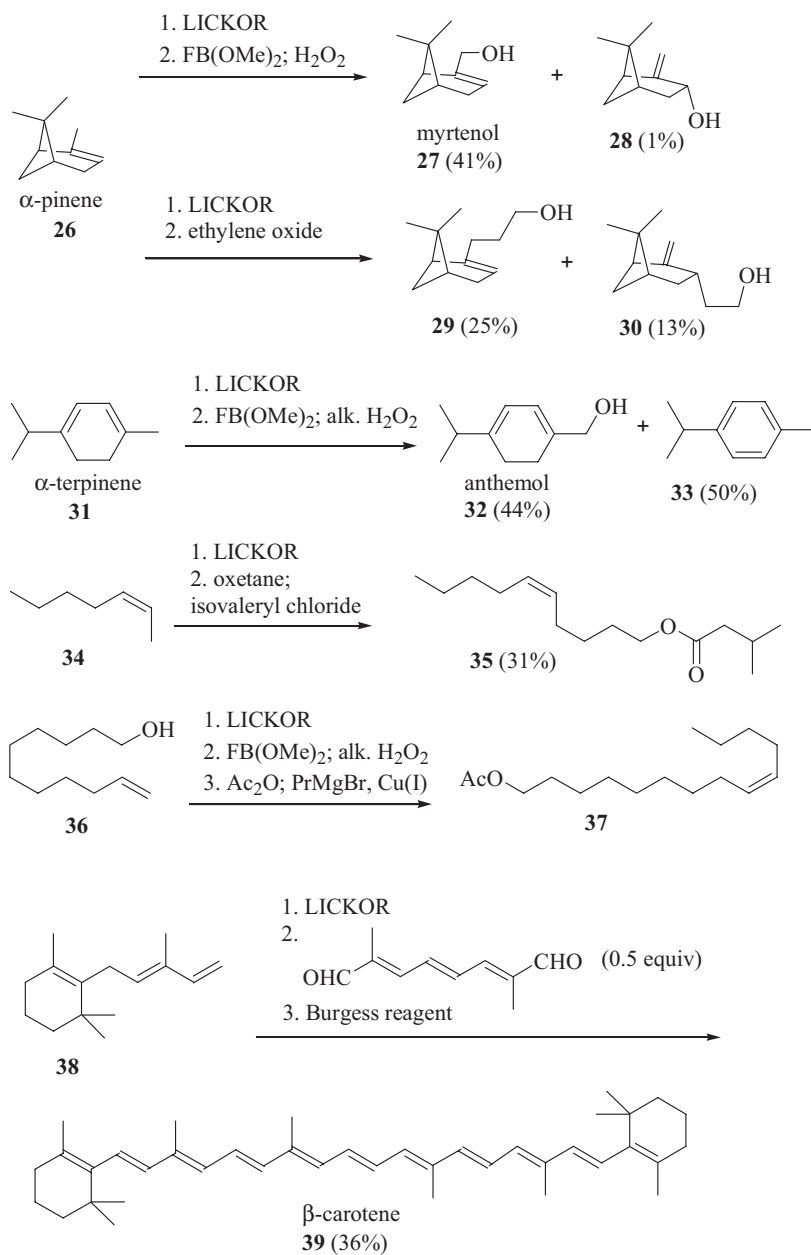
LICKOR deprotonation provides a convenient method for the allylic functionalization of simple alkenes. *cis*-2-Butene, **14**, is the starting material for the preparation of *Z*-crotylboranes such as **15** [12,13], whereas *trans*-2-butene **16** leads to the *E*-crotylborane **17** (Table 1). The LICKOR method was instrumental in the development of enantiomerically and geometrically pure crotylboranes as reagents for asymmetric synthesis. The LICKOR deprotonation of allylsilanes is facile and provides a general route to *E*-vinylsilanes, as in the conversion of **18** to homoallylic alcohol **19** [14]. Because allylsilanes themselves are available from the LICKOR functionalization of alkenes, the procedure can be applied in sequence. Thus, starting from 5-hexen-1-ol **20**, allylsilane **21** was obtained in the first LICKOR reaction [15]. Subsequent LICKOR deprotonation of **21**, trapping with FB(OMe)₂, and oxidation gave diol **22**. The LICKOR method was recently used in the allylic alkylation of 1,5-cyclooctadiene **23** to afford products such as **24** [16]. Yields were lower and the product contaminated by other isomers if other bases, for example BuLi or BuLi/TMEDA, were used. Application of this method with chloromethylpolystyrene resin (Merrifield resin) provided immobilized 1,5-cyclooctadiene **25** which, on hydroboration, furnished a polymer-supported version of 9-BBN [17].

In natural products synthesis, allylic LICKOR functionalization has played a role in both their derivatization and as key steps in total synthesis. Reaction of the anion generated from α -pinene **26** with fluorodimethoxyboron and oxidation predominantly yielded myrtenol **27** and a trace of the isomer **28** [17], whereas alkylation with the larger electrophile ethylene oxide gave a mixture of **29** and **30** (Scheme 5). α -Terpinene **31** is a rare example in which methyl deprotonation and oxidation to anthemol **32** was accompanied by competing methylene deprotonation and elimination to give *p*-cymene **33** [18]. Starting from *Z*-2-heptene **34**, LICKOR functionalization and acylation completed a short synthesis of **35**, the sex pheromone of the moth *Nudarelia cytherea cytherea* [1], whereas a sequence from 10-undecen-1-ol **36** resulted in the synthesis of **37**, the sex attractant of *Spo-doptera frugiperda* [19]. An impressive 2:1 addition of a carbanion generated by

LICKOR from triene **38** has featured in the total synthesis of highly unsaturated polyenes such as β -carotene **39** [20].

Table 1. Examples of LICKOR deprotonation in allylic functionalization.

Starting material	Electrophile	Product (% yield)	Ref.
 14	$\text{Ipc}_2\text{BOMe};$ $\text{BF}_3 \cdot \text{Et}_2\text{O}$	 15	12
 16	$\text{Ipc}_2\text{BOMe};$ $\text{BF}_3 \cdot \text{Et}_2\text{O}$	 17	12
 18	HCHO	 19 (69%)	14
 20	TMSCl	 21 (95:5 <i>Z/E</i>)	15
 21	$\text{FB(OMe)}_2;$ alk. H_2O_2	 22	15
 23		 24 (62%)	16
 23	 (Merrifield resin)	 25 (89% by residual Cl microanalysis)	17



Scheme 5. Examples of LICKOR deprotonations applied to natural product synthesis.

Experimental

4-Trimethylsilyl-(*E*)-but-3-en-1-ol (19)

Precooled (-75°C) THF (25 mL), allyltrimethylsilane **18** (4 mL, 25 mmol), and potassium *t*-butoxide (3.1 g, 28 mmol) were consecutively added to BuLi (28 mmol) from which hexanes had previously been evaporated. As soon as the alkoxide had dissolved, with gentle shaking, the mixture was left to stand for 1 h at -50°C . The reaction mixture was then cooled to -75°C and monomeric formaldehyde in THF (30 mmol, 0.8 M) was added. The red reaction mixture slowly lost its color. After 1 h at room temperature the solvent was evaporated and the reaction quenched by addition of saturated aqueous NH_4Cl (20 mL). After extraction with ether (3×30 mL) the combined organics were washed with brine (20 mL, twice), concentrated, and distilled to give 2.5 g (69 %) product **19**, b.p. 50 – 55°C , 2 Torr. ^1H NMR (CDCl_3 , 400 MHz): δ 6.00 (1H, dt, $J = 18.6$, 6.3 Hz), 5.78 (1H, dt, $J = 18.6$, 1.4 Hz), 3.69 (2H, t, $J = 6.3$ Hz), 2.39 (2H, qd, $J = 6.4$, 1.4 Hz), 1.50 (1H, br s), 0.06 (9H, s).

2-(2,6-Cyclooctadienyl)-1-ethanol (24)

t-Butyllithium (6 mmol in pentanes) was transferred to a Schlenk vessel by means of a cannula, under an argon atmosphere, and the solvent was cautiously removed in vacuo. The resulting white powder was redissolved in anhydrous THF (50 mL) precooled to -78°C , followed by addition of potassium *t*-butoxide (0.672 g, 6 mmol) in THF solution cooled to -95°C and dropwise addition of 1,5-cyclooctadiene **23** (0.655 g, 6.06 mmol). The reaction mixture was stirred gently for 2 h, maintaining the reaction temperature between -78 and -95°C , to give an orange-red suspension. Ethylene oxide (0.29 g, 6.6 mmol) was then added dropwise with stirring, and the reaction mixture was maintained at -95°C for another hour before warming to ambient temperature over 1 h. The reaction mixture was quenched by transfer to a stirred solution of saturated aq. NH_4Cl , and the phases were separated. The aqueous phase was extracted with diethyl ether, and the combined extracts were dried over MgSO_4 , concentrated, and purified by column chromatography on silica (eluent 20 % ethyl acetate in hexane, $R_F = 0.3$) to give 0.566 g (62 %) product **24** as a colorless oil. ^1H NMR (CDCl_3 , 300 MHz): δ 5.55 (3H, m), 5.35 (1H, dd, $J = 6.9$, 11.5 Hz), 3.68 (2H, t, $J = 6.6$ Hz), 2.92 (1H, dd, $J = 5.8$, 11.9 Hz), 2.53 (1H, m), 2.33 (4H, m), 2.2 (2H, m), 1.64 (2H, m).

1.2.2

Heterogeneous C–H Transformation with Solid Superbases

Stefan Kaskel

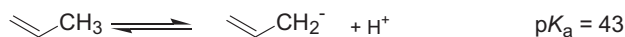
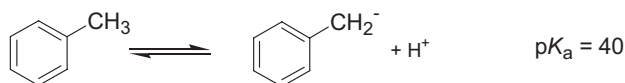
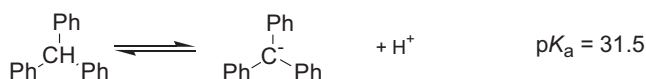
1.2.2.1 Introduction and Fundamental Examples

Whereas solid acid catalysts (zeolites) have been intensively studied, only recently has the use of basic solid catalysts received substantial interest for production of intermediate and fine chemicals [1]. Heterogeneous catalytic transformations are environmentally friendly compared with processes requiring neutralization and

stoichiometric use of bases. The latter is the major source of waste production [2, 3]. Generally, the C–H bond is considered to be non-polar and thus only substrates with electron-withdrawing groups have C–H acidity. Such substrates are transformed in condensation and addition reactions such as the Knoevenagel reaction and Michael addition reaction. For alkanes and unsaturated hydrocarbons such as alkenes and substituted arenes, C–H acidity is low and typically the pK_a relative to water covers a range from 25 to 51. It is, however, possible to deprotonate such hydrocarbons using extremely strong bases, called superbases. In heterogeneous catalysis, the catalyst is not dissolved in the same phase as the reactants and thus it is not possible to directly measure the pK_a of the basic catalyst. Instead, the basic strength of a surface is expressed using a Hammett acidity function H_- :

$$H_- = pK_a + \log \frac{[A^-]}{[AH]}$$

in which $[AH]$ and $[A^-]$ are, respectively, the concentration of an indicator AH and its conjugated base, and pK_a is the negative logarithm of the dissociation constant of that indicator, a weak acid AH and either AH or A^- is colored [4–6].

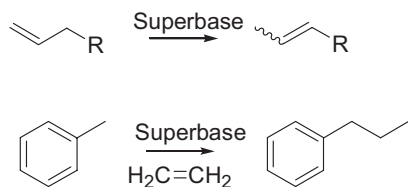


Scheme 1. Deprotonation equilibria for some sp^3 -hybridized carbon atoms and the corresponding equilibrium constants.

Solid bases with $H_- > 26$ are called superbases. Suitable color indicators for solid superbases are 4-chloroaniline ($pK_a = 26.5$) [4], diphenylmethane ($pK_a = 35$), or cumene ($pK_a = 37$) [7]. Another method of characterization of superbasic sites is the use of test reactions [8], spectroscopic techniques [9], or CO_2 adsorption [10].

Solid superbases can deprotonate alkenes in the allylic position and alkyl benzenes (toluene) in the benzylic position. Typical pK_a values of some organic molecules are given in Scheme 1 [11]. However, these values are only approximations, because pK_a values of such highly basic compounds are indirectly adapted to the

acidity scale in water or derived by hydrogen isotope-exchange experiments and thus may differ substantially. Thus, depending on the method used for determination, pK_a values of 35.5, 39.6, and 41.2 have been reported for toluene [12]. Higher acidity (smaller pK_a) is not necessarily associated with a higher rate of deprotonation (kinetic acidity) because substitution may stabilize the carbanion but also induce unfavorable steric effects. As a result, kinetic and thermodynamic acidity may even lead to opposite responses to alkyl substitution [13].

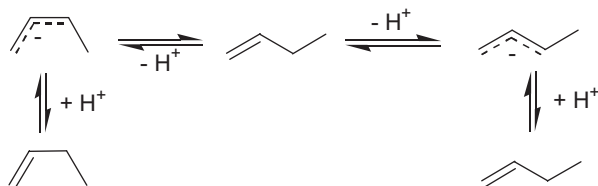


Scheme 2. Superbase-catalyzed isomerization and alkylation.

In comparison with molecular catalysts, solid catalysts can be isolated from the reaction mixtures by filtration or used in continuous processes; this is both environmentally friendly and useful in laboratory-scale experiments. The most important reactions catalyzed by solid superbases are isomerization reactions and the alkylation of substituted arenes in the side chain (Scheme 2). They proceed at room temperature or below with high yield (typically >99 %). The superbase-catalyzed alkylation of aromatic compounds complements the acid-type Friedel–Crafts alkylation and acylation, because the latter results in ring alkylation, whereas the former results in side-chain alkylation.

1.2.2.2 Mechanism

In isomerization reactions, an alkene is deprotonated to form an allyl anion, which is reprotonated to give the more stable alkene (double-bond migration). The most simple example is the isomerization of 1-butene producing a mixture of *cis*- and *trans*-2-butene (Scheme 3). Because the stability of the *cis*-allyl anion formed as an intermediate is greater than for the *trans* form, a high *cis*/*trans* ratio is observed for base-catalyzed reactions whereas for acid-catalyzed reactions the ratio is close to unity. Thus, the *cis*/*trans* ratio of the products has frequently been used as an indication of base-catalyzed reaction mechanisms. The carbanions formed in the course of such superbase reactions are not freely mobile in solution,



Scheme 3. Mechanism of the superbase-catalyzed 1-butene isomerization.

however, but occur as an intermediate bound to a highly basic surface. Little is known about the structure of such surface-bound carbanions. Because several chemically different solid superbase catalysts have been developed, it is to be expected there is no unique mechanistic model but the structure of the surface-bound anion depends on the composition of the catalyst and the structure of the surface.

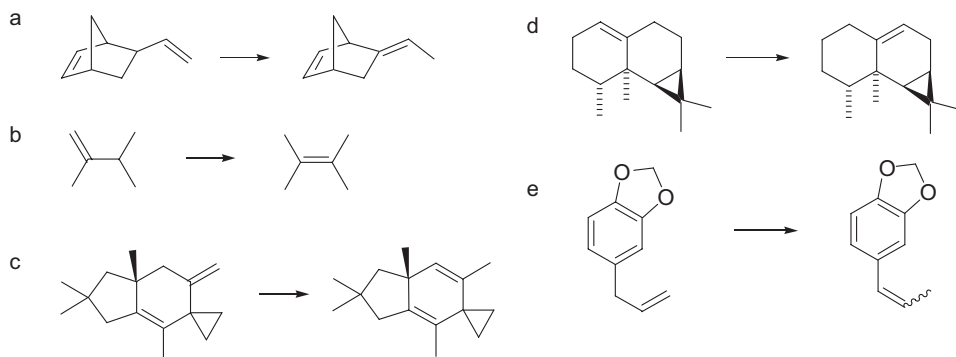
1.2.2.2.1 Catalysts

The most important superbase catalysts are either basic oxides such as MgO with high specific surface area, or alkali metals supported on a basic high surface area material such as Al_2O_3 . The activities of the oxides are in the order $\text{CaO} > \text{SrO} > \text{La}_2\text{O}_3 > \text{MgO}$ [5]. The isomerization of 1-butene over MgO occurs even at 223 K. The activity of such catalysts is critically dependent on the activation procedure, however. MgO catalysts are typically made in the reactor by decomposition of freshly prepared MgCO_3 or $\text{Mg}(\text{OH})_2$ [14, 15]. Highly basic sites are generated at temperatures exceeding 723 K under vacuum. The high-temperature treatment is necessary to remove carbon dioxide, water, and oxygen. On exposure to the atmosphere, basic oxides adsorb carbon dioxide and water. Thus, removal of the adsorbates and consequent handling under inert conditions is required to use superbasic catalysts for isomerization reactions or alkylation. The maximum activity of MgO in the 1-butene isomerization is achieved by activating the catalyst at 800 K in vacuum. A surface model for MgO was discussed in which oxide anions with low coordination numbers (3) were proposed as the most basic sites [5]. The basicity of pure and modified MgO was recently studied by Knözinger using IR spectroscopy [16].

Sumitomo catalysts ($\text{Na}/\text{NaOH}/\text{Al}_2\text{O}_3$) are alkali metals supported on high-surface-area γ -alumina ($100\text{--}200\text{ m}^2\text{ g}^{-1}$) and are typically of higher basicity ($H_- > 37$) [17, 18]. High-surface-area alumina can be prepared from high-surface-area boehmite (SASOL) by heating in dry N_2 at 823 K. Subsequently, alkali metal hydroxide is added at lower temperatures (typically the melting point of the corresponding alkali metal oxide) and in the last step, the alkali metal is added. After homogenization, the system is cooled to room temperature and the reactants are added, usually without any solvent. X-ray photoelectron spectroscopy in combination with secondary-ion mass spectrometry and X-ray absorption fine structure indicates that in the first reaction of alumina with the hydroxide an aluminate with cationic vacancies is formed. Subsequently added alkali metal occupies the cationic vacancies and donates electrons to the surface oxygen atoms and thus increases their charge to exhibit superbasicity [9]. Highly basic catalysts are also obtained from the decomposition of alumina-supported cesium acetate [7], KNO_3 , or K_2CO_3 [19].

Alkali metals can also be loaded on to supports from ammoniacal solutions [20, 21]. The metal is either directly dissolved in liquid ammonia at 233 K together with the solid support ($\text{M}(\text{NH}_3)/\text{Al}_2\text{O}_3$) or a trace amount of Fe_2O_3 is added catalyzing the decomposition of the ammoniacal $\text{M}(\text{NH}_3)$ solution to form the corre-

sponding amide ($\text{MNH}_2/\text{Al}_2\text{O}_3$). After evaporation of the NH_3 , a bluish ($\text{M}(\text{NH}_3)/\text{Al}_2\text{O}_3$) or grayish ($\text{MNH}_2/\text{Al}_2\text{O}_3$) powder is obtained. During activation of the catalyst at 573 K, the amide is decomposed and forms an unknown surface site that is highly basic. Such catalysts are typically pyrophoric and should be carefully handled under inert conditions. $\text{KNH}_2/\text{Al}_2\text{O}_3$ catalysts have isomerization activity at temperatures as low as 200 K. The activity of $\text{K}(\text{NH}_3)/\text{Al}_2\text{O}_3$ is slightly lower than that of $\text{KNH}_2/\text{Al}_2\text{O}_3$. $\text{KNH}_2/\text{SiO}_2$ and $\text{KNH}_2/\text{TiO}_2$ are totally inactive. K/MgO has been used for the alkylation of aromatic hydrocarbons [22]. Highly basic catalysts are obtained from ammoniacal solutions of alkali metals in the presence of high-surface-area silicon nitride (Si_3N_4) [23]. In contrast with alumina, silicon nitride-based materials can be obtained in a porous form with high accessible surface area and well defined pore size distribution [24–27]. Microporous ($d < 2$ nm) silicon nitride is obtained by using a template-assisted synthesis [24]. Mesoporous materials ($d = 5.6$ nm) are made from silicon halides and ammonia [25, 26]. Tailoring of the pore size can be used to adjust the selectivity of such superbases. For example, a microporous catalyst selectively transforms the smaller alkene in a 1:1 mixture of 1-hexene and 1-hexadecene whereas on a mesoporous catalyst both substrates are converted with comparable reaction rates [24]. Similar size-dependent reaction rates are observed in side-chain alkylation reactions of arenes. Thus, porous silicon nitride-based catalysts have size-exclusion selectivity similar to shape-selectivity effects observed in zeolite catalysis.



Scheme 4. Examples for the superbase-catalyzed alkene isomerization.

Microporous superbasic catalysts based on zeolites suitable for alkene isomerization were developed by Martens et al. [28–30]. They have high activity in the 1-butene isomerization and side-chain alkenylation of xylene [31], and are prepared by impregnating a dehydrated zeolite (NaY) with NaN_3 in alcoholic solution. Subsequent decomposition of the azide inside the zeolite pores produces metallic sodium particles Na_x^0 and cationic sodium clusters Na_4^{3+} . The high catalytic activity was attributed to the ionic sodium clusters as they could be detected using ESR spectroscopy.

Alkali metals supported by nanoporous carbons were proposed by Stevens et al. as non-pyrophoric solid-base catalysts with high activity in 1-butene isomerization and side-chain alkylation of toluene with propene [32, 33].

1.2.2.3 Scope and Limitations

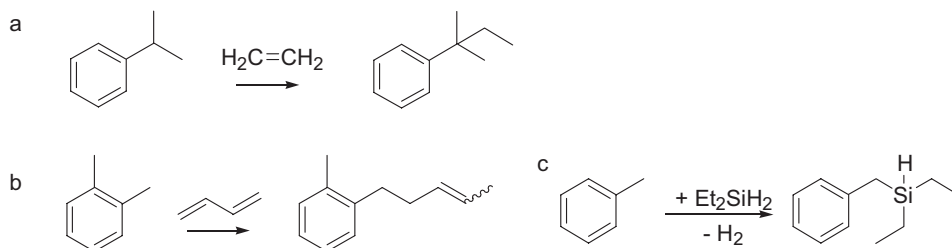
1.2.2.3.1 Isomerization Reactions

The most important industrial application is the so called Sumitomo process in which 5-vinylbicyclo[2.2.1]hepta-2-ene (vinyl norbornene) is converted to 5-ethylidene[2.2.1]hepta-2-ene (ethylidene norbornene) (Scheme 4, a) [34, 35]. The product is used as a comonomer for the production of polymers on a 2000 t/year scale. The advantage of the superbase catalyst is the high activity at low temperature (243 K), and the high selectivity of 99.8 % at 99.7 % conversion. Acidic catalysts cause side-reactions such as ring opening and are not economic. The isomerization of 2,3-dimethylbutene-1 to 2,3-dimethylbutene-2 was also proposed in industrial applications for the production of synthetic pyrethroids (Scheme 4, b) [34, 35]. The double-bond migration was also successfully applied to more complex structures such as pinene, protoilludene, illudadiene (Scheme 4, c) [5] and calarene (Scheme 4, d) [36]. These alkenes contain three-membered rings and acidic catalysts would initiate ring-opening reactions. Thus, superbase catalysis plays an important role in the production of fine chemicals such as terpenes in the fragrance industry [37]. Because of the high basicity of the catalysts, however, the methods are limited to substrates without acidic functional groups and careful drying is necessary. Heteroatoms in the substrate are tolerated. For example, the isomerization of safrole to isosafrole proceeds at 300 K over Na/NaOH/Al₂O₃ (Scheme 4, e). Superbase catalysts have also been used in the isomerization of olefinic amines such as *N,N*-diethyl-3,7-dimethyl-octa-2(*Z*),6-dienylamine to *N,N*-diethyl-3,7-dimethyl-octa-1(*E*),3-dienylamine [38]. Subsequent hydrolysis of the resulting enamine can be used to generate dihydrocitrinal in 86 % yield. In a similar way, allyl ethers are converted into vinyl ethers over solid superbases [37, 39].

1.2.2.3.2 Alkylation Reactions

The second important use of superbases is side-chain alkylation of aromatic compounds [22, 34]. In these reactions a benzyl anion generated by the superbase catalyst subsequently attacks olefins such as ethene or propene as a nucleophile. The result of such a nucleophilic addition of a carbanion is side-chain alkylation of the arene by ethene. The reaction was commercialized by Sumitomo for the side-chain alkylation of cumene (Scheme 5, a) [34].

Production of *t*-amylbenzene proceeds at 313 K with high conversion (99.9 %) and selectivity (99.6 %). Another commercial application is the Amoco process for production of polyester intermediates such as 2,6-naphthalenedicarboxylic acid (NDA) [34]. NDA is produced in a 45 000 t year⁻¹ plant at Decatur, Alabama, USA. In the first reaction step, *o*-xylene is reacted with butadiene to form 5-(*o*-tolyl)-2-



Scheme 5. Examples of the superbases-catalyzed side chain alkylation.

pentene (Scheme 5, b) [35]. Alkylation of toluene with ethene simultaneously results in mono-, di-, or trialkylated products [22]. The ratio depends on the ethene pressure and temperature used. Higher temperatures and pressures favor multiple alkylation. Propylation is usually more demanding and requires higher temperatures and pressures [22]. The benzylic activation has also been used for nucleophilic substitution at silicon over superbasic $\text{KNH}_2/\text{Al}_2\text{O}_3$ catalysts [40]. The latter is a method for Si–C bond formation, for example for the coupling of toluene and diethylsilane (Scheme 5, c).

Experimental

All operations are performed in an argon filled glove box ($\text{O}_2 < 1\text{ppm}$, $\text{H}_2\text{O} < 1\text{ppm}$) or a vacuum line.

Preparation of the Catalyst

Typically, 100 mg support (Degussa Al_2O_3 , type C, $S_g = 100\text{ m}^2\text{ g}^{-1}$ dried at 773 K in vacuum before use or amorphous Si_3N_4 , $S_g = 700\text{ m}^2\text{ g}^{-1}$ [23, 26]) with the desired amount of potassium (10 mg for Al_2O_3 , 30 mg for Si_3N_4) and a trace amount of Fe_2O_3 (1 mg) are loaded in a Schlenk tube reactor. At 233 K, 3 mL ammonia (UHP, Messer) are condensed in the reactor. The blue solution turns gray after a few minutes. After 1 h the reactor is warmed to room temperature and the ammonia is evaporated. The reactor is placed in a tube furnace and heated to 573–673 K in vacuum (10^{-4} mbar).

DB-1 Isomerization

2,3-Dimethylbut-1-ene (DB-1, Fluka, 98 %) is distilled before use and stored under argon. The alkene (2 mL DB-1) is added to the catalyst at room temperature and stirred. After 10 min the catalyst is separated from the liquid by filtration. Conversion is close to equilibrium (92.8 %). For 1-hexene (vinyl-norbornene) the conversion is 99 % after 10 min (4 h).

Side-chain Alkylation of Toluene

The alkylation is carried out in a 100-mL autoclave. The catalyst (100 mg) is suspended in toluene (10 mL) and the suspension is transferred to the autoclave

under argon. Subsequently, the autoclave is pressurized with ethene (30 bar) and the mixture is stirred for 60 h at room temperature (74 % conversion (toluene), product ratio 3-phenyl pentane/propylbenzene = 1.8:1).

1.2.3

Sequences of Hydro- or Carbometalation and Subsequent β -Hydrogen Elimination

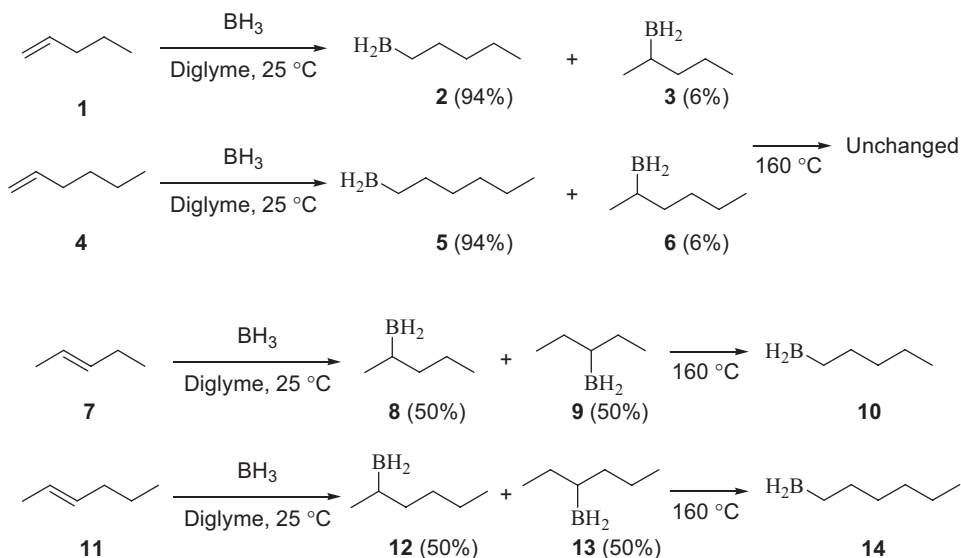
1.2.3.1 Borate Isomerizations

Jesús A. Varela

1.2.3.1.1 Introduction and Fundamental Examples

Organoboranes derived from internal acyclic olefins by hydroboration with BH_3 undergo thermal isomerization at elevated temperature (100–160 °C). The Boron atom readily moves down the chain, past a single branch, but not past a quaternary carbon atom [1].

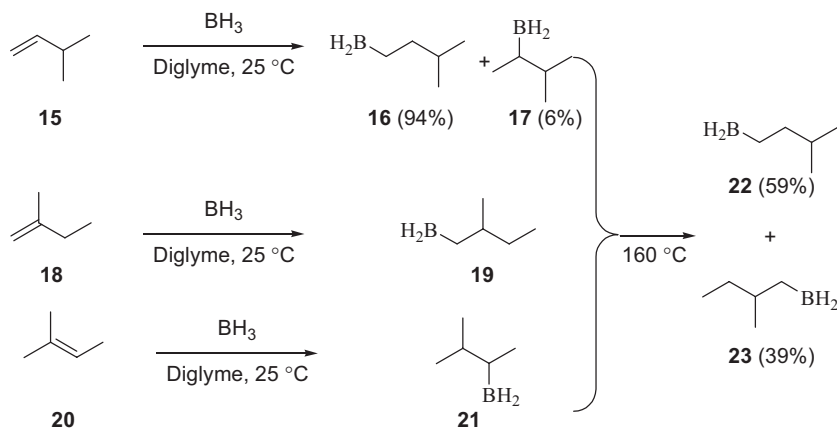
Hydroboration of terminal olefins, such as pent-1-ene (**1**) and hex-1-ene (**4**), places 94 % of the boron at the primary (**2**, **5**) position and 6 % at the secondary (**3**, **6**) position. Isomerization of these organoboranes for 4 h at 160 °C gives essentially the same distribution. The organoboranes derived from pent-2-ene (**7**) and hex-2-ene (**11**), with an initial boron distribution close to 50:50 between the 2 (**8**, **12**) and 3 (**9**, **13**) positions isomerize rapidly to place the boron predominantly (91–95 %) at the terminal position (**10**, **14**, Scheme 1).



Scheme 1. Isomerization of organoboranes derived from straight-chain olefins.

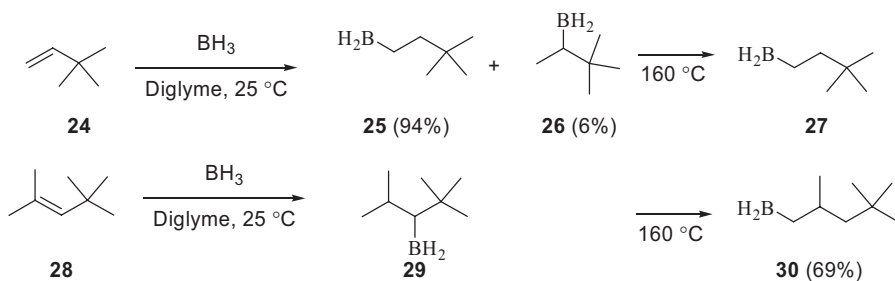
Hydroboration of 3-methylbut-1-ene (**15**) gives 94 % of the primary (**16**) and 6 % of the secondary (**17**) organoborane, whereas with the 2-methylbut-1-ene (**18**) essentially only the primary derivative (**19**) is formed. Hydroboration of 2-methyl-

but-2-ene (**20**) affords the secondary organoborane **21** in 98 % yield (Scheme 2). Isomerization of the organoboranes derived from these three individual olefins by heating for 4 h at 160 °C results in a nearly identical boron distribution about the chain, with 59 % ending up at the less hindered primary position (**22**) and 39 % ending up at the more hindered position (**23**). The preference of the boron atom for the less crowded of the two primary positions is attributed to the operation of steric factors (Scheme 2).



Scheme 2. Isomerization of organoboranes derived from singly branched olefins.

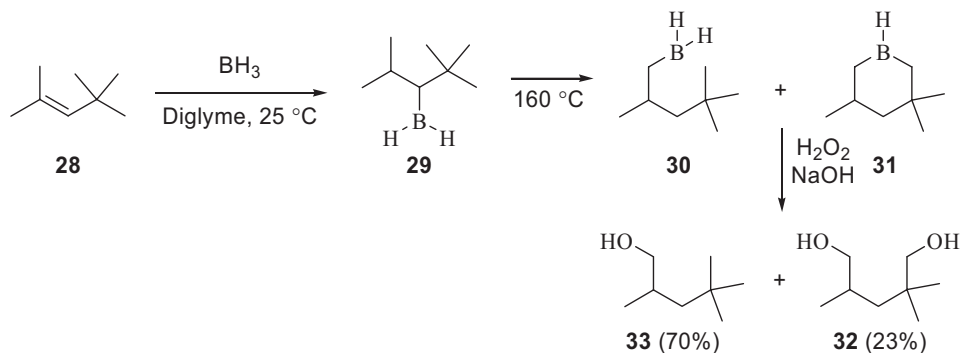
3,3-Dimethylbut-1-ene (**24**), with an initial boron distribution of 94 % primary (**25**) and 6 % secondary (**26**), undergoes isomerization to essentially pure primary organoborane **27**. Exceedingly rapid migration of the boron from the internal **29** to the terminal position **30** occurs in the isomerization of the borane derivative from 2,4,4-trimethylpent-2-ene (**28**). These results clearly establish that the boron atom readily migrates past a single branch, but not past a double branch (Scheme 3).



Scheme 3. Isomerization of organoboranes derived from doubly branched olefins.

The low yield observed in the isomerization of the 2,4,4-trimethylpent-2-ene (**28**) is because of the facile cyclization of the borane **30**, with evolution of hydrogen, to produce a boron heterocycle **31**. Oxidation of the reaction mixture provides

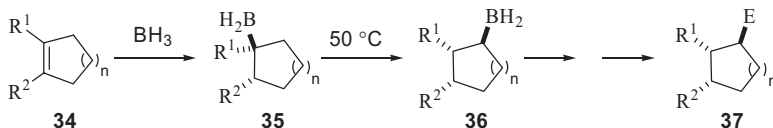
2,2,4-trimethylpentane-1,5-diol (**32**) and 2,4,4-trimethylpentan-1-ol (**33**) (Scheme 4) [2].



Scheme 4. Isomerization-cyclization of (2,2,4-trimethyl-3-pentyl)borane (**29**).

These results reveal that under isomerization conditions boranes with five carbon atoms or more undergo intramolecular cyclization to produce the boron heterocycle and hydrogen. The reaction is specially facile when the primary hydrogen is available at the 5 position [3].

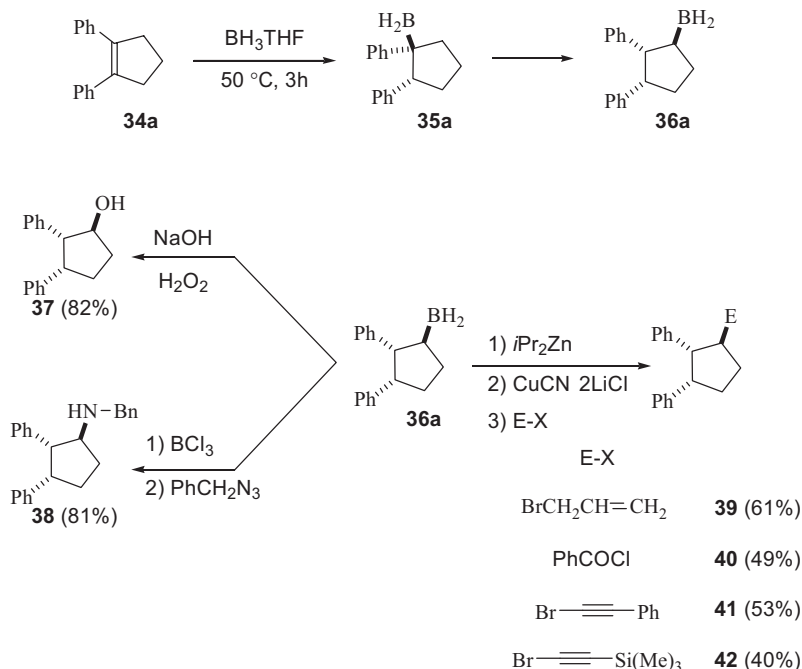
It was noticed by Rickborn and Wood [4] and Field and Galagher [5] that cyclic tetrasubstituted alkenes undergo such a isomerization under much milder conditions. This approach enables highly stereoselective conversion of a variety of cyclic tetrasubstituted alkenes of type **34** into polyfunctional products of type **37** in one-pot reactions via the intermediate organoboranes **35** and **36** (Scheme 5) [6–8].



Scheme 5. Allylic C–H activation via hydroboration of cyclic tetrasubstituted alkenes.

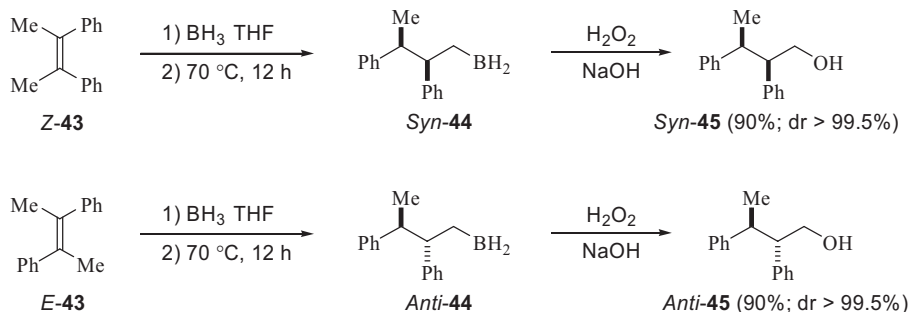
This rearrangement of tertiary alkylboranes enables highly stereoselective C–H activation of allylic positions and thus the construction of three adjacent stereocenters. For example, 1,2-diphenylcyclopentene (**34a**) was smoothly hydroborated with $\text{BH}_3\cdot\text{THF}$ (THF, 50°C , 3h) to provide the tertiary alkylborane **35a**, which undergoes a stereoselective syn migration leading to the less sterically hindered secondary organoborane **36a** (Scheme 6). Oxidation of **36a** with 30% H_2O_2 affords the cyclopentanol **37** in 82% overall yield as single stereoisomer. Treatment of **36a** with boron trichloride then benzyl azide provides de amine **38** as one stereoisomer in 81% overall yield. Transmetalation of **36a** to the corresponding organozinc compound by treatment with $i\text{Pr}_2\text{Zn}$ (2 equiv.) and subsequent transformation to the zinc–copper reagent by addition of $\text{CuCN}\cdot 2\text{LiCl}$ furnishes, after reaction with electrophiles such as allyl bromide, benzoyl chloride, 2-phenylethynyl bromide, or

1-bromo-2-trimethylsilylacetylene, the expected products **39–42** with diastereomeric excesses greater than 97 % and in 40–61 % overall yield (Scheme 6).



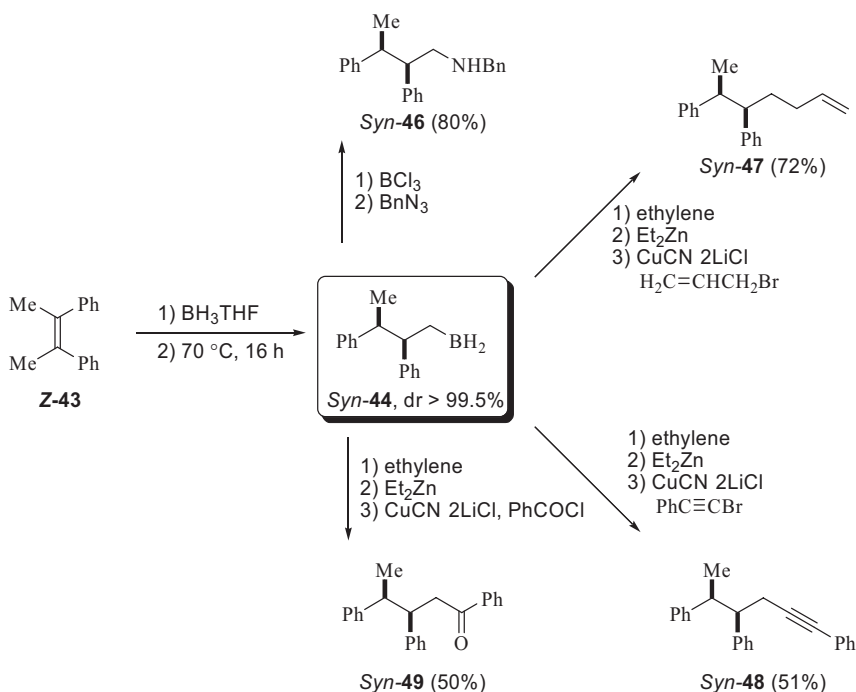
Scheme 6. Transformation of cyclic borane **36a**.

This rearrangement can be also performed with acyclic tetrasubstituted olefins, enabling control of two adjacent carbon centers. Thus, hydroboration of *Z*- and *E*-2,3-dimethylstilbene (**43**) with $\text{BH}_3\cdot\text{THF}$ and subsequent heating at 70°C for 12 h furnishes stereoselectively the syn and anti organoboranes **44**, which after oxidative workup provide the corresponding alcohols *syn*-**45** and *anti*-**45** in 90 % yield and $\text{dr} > 99.5\%$ (Scheme 7) [7–9].



Scheme 7. Allylic C–H activation via hydroboration of acyclic tetrasubstituted olefins.

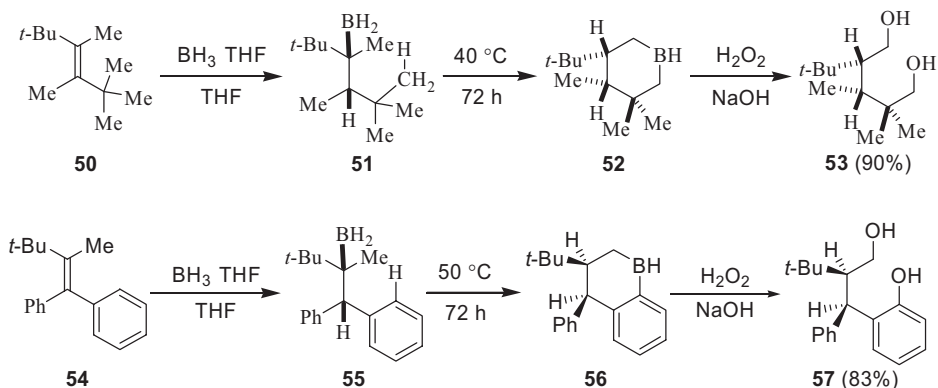
Similarly to the cyclic tetrasubstituted olefins, the resulting organoboranes *syn*-**44** and *anti*-**44** can be converted into a variety of organic products. Thus, the reaction of *syn*-**44** with BCl_3 (4 equiv.) in CH_2Cl_2 followed by the reaction with benzyl azide furnishes the amine *syn*-**46** in 80 % yield. The organoborane *syn*-**44** is converted to the corresponding diethylborane derivative by bubbling ethylene through the reaction mixture. This compound undergoes smooth transmetalation to the corresponding zinc derivative by reaction with diethylzinc (10 equiv., 0°C , 3 h). This mixed diorganozinc can be further converted to the corresponding zinc–copper derivative, by addition of $\text{CuCN}\cdot\text{LiCl}$, and reacted with allyl bromide, leading to the desired allylated product *syn*-**47** in 72 % yield. Its reaction with 2-bromo-1-phenylacetylene provides the cross-coupling product *syn*-**48** in 51 % yield, and its benzoylation with PhCOCl furnishes, as sole product, the diastereomerically pure ketone *syn*-**49** in 52 % yield. Similarly, the organoborane *anti*-**44** furnishes under the same reaction conditions *anti*-**46** (78 %), *anti*-**47** (68 %), and *anti*-**48** (52 %, Scheme 8) [7–9].



Scheme 8. Transformations of borane *syn*-**44**.

It is also possible to achieve remarkable intramolecular remote C–H activation of sterically hindered tetrasubstituted olefins such as **50** (Scheme 9) [8, 9]. The initial hydroboration of **50** leads to **51**, which gives regio- and stereoselectively the six-membered intermediate organoborane **52**, via a C–H insertion reaction (40°C , 72 h). After oxidation, the diol **53** is obtained in 90 % yield as only one diastereo-

isomer. Similarly, it is possible to achieve remote C–H activation of hindered phenyl substituted olefins such as **54** (Scheme 9) [8–10].



Scheme 9. Remote C–H activation via hydroboration of hindered tetrasubstituted olefins.

1.2.3.1.2 Mechanism

Study of the kinetics of the reaction of the dimer *sym*-tetrasiamyldiborane with olefins has established that the reaction is second order, first order in each component [11]. The hydroboration reaction involves cis addition of the boron–hydrogen linkage to the double bond and the hydroboration reaction is very powerfully catalyzed by ether solvents. Consequently, it was proposed that the hydroboration reaction involved a transition state in which the ether solvent serves to solvate and stabilize the leaving disiamylborane group (Fig. 1) [1].

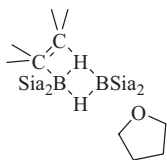
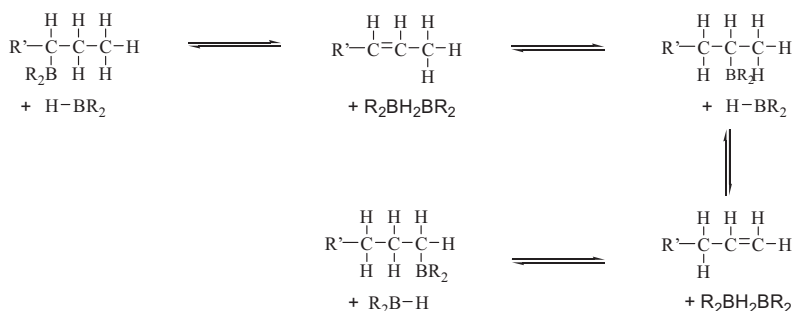


Figure 1. Transition state proposed for the reaction of *sym*-tetrasiamyldiborane with olefins.

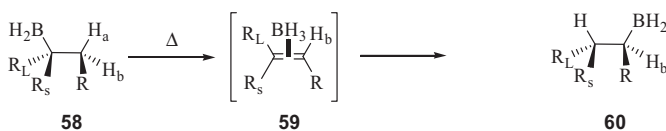
According to this, the presence in the reaction media of a small amount of dialkylborane with the usual trialkylborane, can readily facilitate cis elimination of a dialkylborane moiety, yielding the olefin and the *sym* tetraalkyldiborane (Scheme 10) [1].

The mechanism of the thermal isomerization of organoboranes derived from internal acyclic olefins via hydroboration with BH_3 at elevated temperature seems to involve successive cis eliminations of boron–hydrogen moieties from the initial organoborane, followed by additions, rapidly achieving thermodynamic equilibrium among the possible organoboranes (except where the isomerization involves moving the boron atom past a quaternary carbon). The boron atom ends up preferentially in the less sterically crowded position of the alkyl group.



Scheme 10. Mechanism of thermal isomerization of organoboranes.

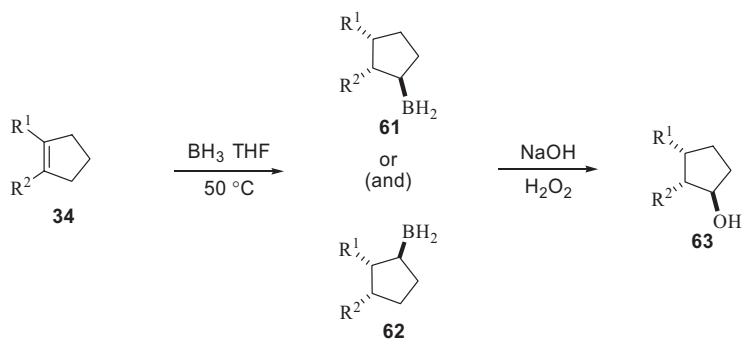
In allylic C–H activation with tertiary alkylboranes **58**, the high stereochemical control is explained by assuming a highly preferential migration of the hydrogen atom H_a (rather than H_b) to form the more stable organoborane **60** via the tentative borane–olefin complex **59**. Migration of H_a leads to the most stable borane–olefin complex **59** (R and R_s are in the cis arrangement) which never dissociates, because this would result in a decrease in stereoselectivity (Scheme 11) [6, 9, 10]. Ab initio calculations have predicted relatively small activation barriers ($\leq 30 \text{ kcal mol}^{-1}$) for dehydrogenation reactions between borane and hydrocarbons that occur via four-center transition states. Even lower activation barriers, and more exothermic reactions, should be observed for donor-substituted arenes. These different reactivities, which can be tuned by the substituents, could provide the basis for selective and directed functionalization of hydrocarbons [12].



Scheme 11. Mechanism of stereoselective allylic C–H activation with tertiary alkylboranes.

1.2.3.1.3 Scope and Limitations

It has been noticed that two intermediate regioisomeric organoboranes **61** and **62** can be obtained from unsymmetrical disubstituted cyclopentenes of type **34** ($R^1 \neq R^2$, Scheme 12). If the difference between the steric hindrance of the two substituents is large, migration occurs preferentially on the side of the least bulky substituent. Thus, 1-*tert*-butyl-2-methylcyclopentene (**34b**) produces only 3-*tert*-butyl-2-methylcyclopentanol (**63a**) in 70 % yield after oxidation (d.r. $\geq 98\%$; Table 1, entry 1) [7, 8]. Interestingly, if the reaction is performed at 65°C instead of 50°C , and with 96 h reaction time, further migration of the boron atom occurs, producing 3-*tert*-butyl-4-methylcyclopentanol (**64**) in 64 % yield as one diastereoisomer (d.r. $\geq 98\%$), showing the importance of temperature control when performing these rearrangements (Table 1, entry 2). The relative stereochemistry of **64** confirms also the suprafacial nature of the boron migration.



Scheme 12. Allylic C–H activation via hydroboration of unsymmetrical cyclic tetrasubstituted alkenes.

Table 1. Thermal rearrangement of organoboranes resulting from the hydroboration of tetrasubstituted cyclopentene derivatives of type **34**.

Entry	Olefin of type 34	Products of type 63	Yield ^a
1	 34b	 63a	70
2	 34b	 64	64 ^b
3	 34c	 65	60 ^c
4	 34d	 63b : 58%	 63c : 12%
5	 34e	 63d : 40%	 63e : 30%

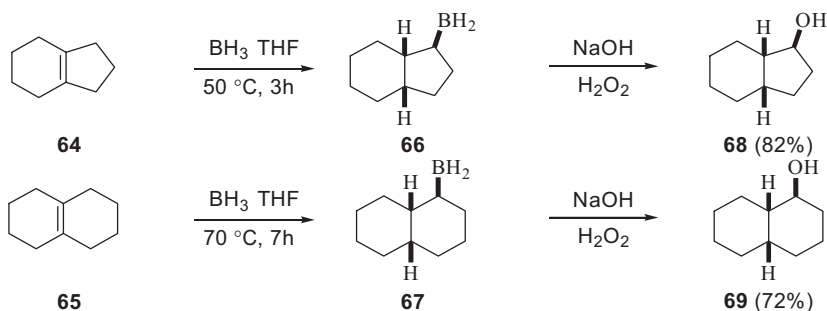
^a Isolated yield of analytically pure compound.

^b The reaction mixture was stirred at 65 °C for 96 h

^c The reaction mixture was stirred at 50 °C for 24 h

Similarly, after 24 h of heating at 50 °C alkenylsilane **34c** affords the double migration product **65** in 60 % yield (Table 1, entry 3). With unsymmetrical cyclopentenones **34d** and **34e** a mixture of migration products in both directions was observed.

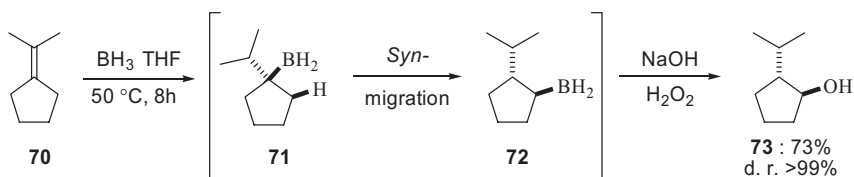
Bicyclic alkenes like **64** and **65** (Scheme 13) also undergo stereoselective migration. The bicyclic olefin **64** reacts similarly to the substituted cyclopentenones at 50 °C within 3 h affording alcohol **68** in 82 % yield after oxidative workup (Scheme 13). The six-membered bicyclic system **65** reacts much more slowly and requires 7 h reaction time at 70 °C, affording, after oxidative workup, the alcohol **69** in 72 % yield (Scheme 13) [6–8].



Scheme 13. Allylic C–H activation via hydroboration of bicyclic tetrasubstituted alkenes.

Interestingly, the migration occurs almost exclusively in the direction of the five-membered ring. This may be because appropriate alignment of the adjacent C–H bond with the C–B bond in the five-membered ring facilitates dehydroboration. In a six-membered ring, there would be an angle of approximately 60 °C between the C–H and C–B bonds; this alignment would require a higher energy of activation.

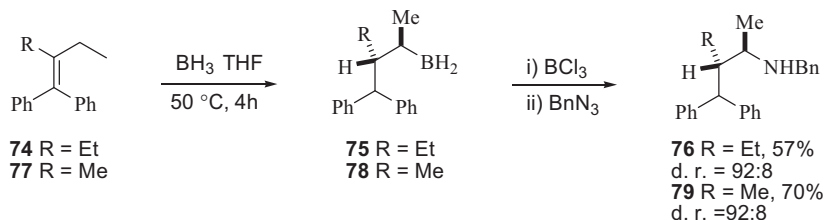
Hydroboration of exo-alkylidene cyclopentane derivatives, for example **70**, also proceeds smoothly (BH_3 , THF, 50 °C, 8 h) leading to the migration product in the cyclopentane ring only and affording the trans alcohol **73** after oxidation of the organoborane **72** obtained by syn migration of the intermediate tertiary organoborane **71** (Scheme 14) [7–9].



Scheme 14. Allylic C–H activation via hydroboration of exo-alkylidene cyclopentane derivatives.

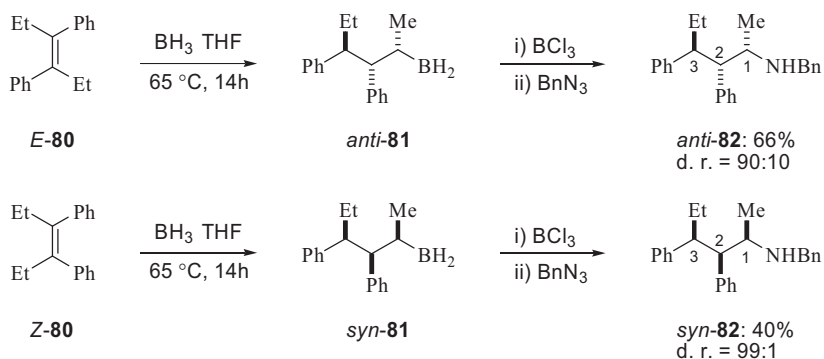
As for tetrasubstituted double bonds bearing methyl substituents (Scheme 7), migration toward higher alkyl substituents is much faster than toward methyl groups. If the alkyl substituent bears diastereotopic hydrogen atoms migration

will be diastereoselective. Thus, heating 2-ethyl-1,1-diphenylbut-1-ene (**74**) with $\text{BH}_3 \cdot \text{THF}$ for 4 h at 50°C produces the organoborane **75** which, after treatment with BCl_3 at room temperature for 4 h then with BnN_3 from 0 to 25°C overnight, affords the benzylamine **76** (57 % yield) in a d.r. of 92:8 (Scheme 15). A similar result was obtained starting with 2-methyl-1,1-diphenylbut-1-ene (**77**), which provides, after amination of the intermediate organoborane **78**, the expected benzylic amine **79** in 70 % yield (d.r. = 92:8, Scheme 15) [7, 13].



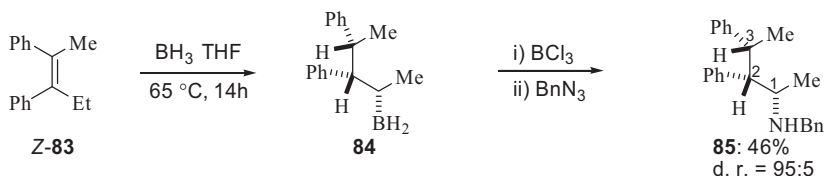
Scheme 15. Allylic C–H activation via hydroboration on side-chains bearing diastereotopic substituents.

This reaction also proceeds well with a variety of other substituted stilbene derivatives. Thus, the boranes obtained by hydroboration of *E* and *Z* stilbenes **80** undergo the thermal boron migration with excellent diastereoselectivity leading to the anti and syn organoboranes **81**. After amination of **81** the corresponding benzylic amines (anti and syn **82**) were obtained in 66 and 40 % yield and with diastereoselectivity better than 90:10 between C(1) and C(2) (Scheme 16) [7, 8, 13].



Scheme 16. Allylic C–H activation via hydroboration of substituted stilbene derivatives.

Remarkable regioselectivity was observed in the thermal migration of the tetra-substituted alkene **Z-83**. Hydroboration of this compound furnishes only the migration product in the direction of the ethyl group. Furthermore, the migration was stereoselective providing, after the standard amination sequence, the benzylic amine **85** in 46 % yield. The diastereoselectivity was 95:5 between C(1) and C(2) and >99:1 between C(2) and C(3) (Scheme 17) [7, 8, 13].



Scheme 17. Allylic C–H activation via hydroboration of an ethyl vs. a methyl group.

Experimental

2,3-Diphenylcyclopentanol (37)

To a solution of 1,2-diphenylcyclopentene (**34a**) (0.220 g, 1 mmol) in THF (4 mL) was slowly added $\text{BH}_3\text{.THF}$ (3 mL, 3 mmol, 1 M in THF) at 0 °C. The resulting solution was stirred for 3 h at 50 °C. After cooling of the solution to 0 °C, NaOH (4 mL, 2 M in H_2O) and H_2O_2 (4 mL, 30 % in H_2O) were slowly added. The resulting solution was stirred for 2 h at 25 °C. The aqueous phase was extracted with ether (2 × 20 mL) and the combined organic phases were washed with water and brine and dried over MgSO_4 . After evaporation of the solvent the crude product was purified by column chromatography (pentane– Et_2O , 1:1) affording the desired alcohol **37** as one diastereoisomer (0.195 g, 82 %). IR (film): 3351, 3028, 2956, 1603, 1497, 1451, 698 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz): δ = 7.13–7.02 (m, 6H), 6.84–6.76 (m, 4H), 4.70–4.63 (m, 1H), 3.75–3.67 (m, 1H), 3.35 (dd, J = 8.0, 6.2 Hz, 1H), 2.58–2.47 (m, 1H), 1.96–1.84 (m, 1H), 2.38–2.26 (m, 1H), 2.18–2.05 (m, 1H), 1.96–1.84 (m, 1H), 1.72 (s, 1H); ^{13}C NMR (CDCl_3 , 75 MHz): δ = 141.9, 139.4, 128.7, 128.4, 127.7, 127.6, 126.1, 125.8, 77.2, 59.6, 48.5, 33.6, 28.3; MS (EI): 238 (17, M^+), 220 (100), 147 (38), 129 (47), 91 (44); HRMS calcd for $\text{C}_{17}\text{H}_{18}\text{O}$: 238.1358, found: 238.1362.

N-Benzyl-2,3-diphenylbutan-1-amine (*syn*-46)

$\text{BH}_3\text{.THF}$ (3 mL, 3 mmol, 1 M in THF) was slowly added at 0 °C to a solution of Z-1,2-dimethyl-1,2-diphenylethylene (**Z-43**) (0.208 g, 1 mmol) in THF (4 mL). The resulting solution was stirred under reflux for 16 h. The solvent and excess of borane were removed under reduced pressure (0.1 mm Hg, 1 h). The residue was dissolved in CH_2Cl_2 (2 mL) and BCl_3 (5 mL, 5 mmol, 1 M in CH_2Cl_2) was added at 0 °C. After stirring for 4 h at 25 °C, the solvent and excess BCl_3 were removed under reduced pressure (0.1 mm Hg, 1 h). The residue was dissolved in CH_2Cl_2 (2 mL) and benzyl azide (0.399 g, 3 mmol) was added at 0 °C. The solution was left to warm to 25 °C overnight. The reaction was then quenched with NaOH (2 M in H_2O). The aqueous phase was extracted with ether (2 × 20 mL) and the combined organic phases were washed with water and brine and dried over MgSO_4 . After evaporation of the solvent, the crude product was purified by column chromatography (pentane– Et_2O = 3:1) affording the desired amine *syn*-46 as one diastereoisomer (0.251 g, 80 %). IR (film): 3308, 3084, 3026, 2966, 2026, 1494, 1452, 775, 756 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz): δ = 7.33–6.92 (m, 15H), 3.62 (d, J = 13.4 Hz,

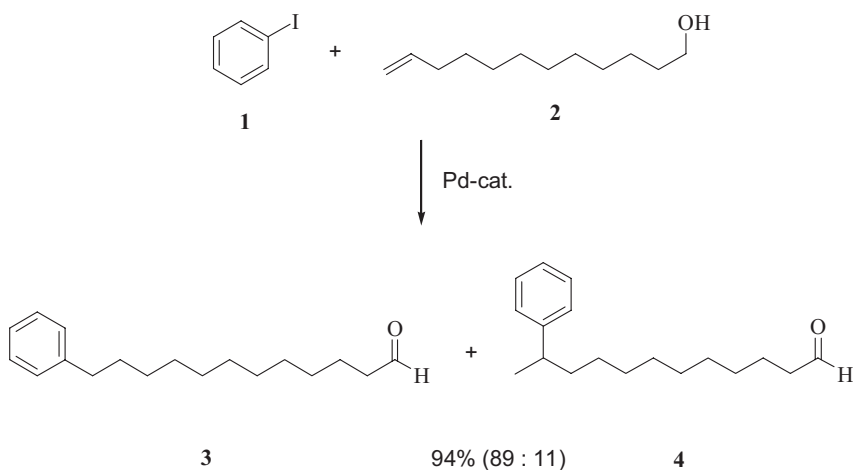
1H), 3.42 (d, $J = 13.4$ Hz, 1H), 3.00 (dt, $J = 10.1, 4.3$ Hz, 1H), 2.91–2.80 (m, 1H), 2.70 (dd, $J = 11.7, 9.9$ Hz, 1H), 2.59 (dd, $J = 11.7, 4.3$ Hz, 1H), 0.98 (d, $J = 7.8$ Hz, 3H); ^{13}C NMR (CDCl_3 , 75 MHz): $\delta = 145.9, 142.4, 139.8, 128.6, 128.5, 128.4, 128.2, 127.9, 127.4, 126.8, 126.7, 126.3, 53.5, 53.0, 52.9, 44.5, 21.0$; MS (EI): 313 (3, M^+), 195 (3), 121 (18), 120 (100), 105 (20), 91 (97), 43 (9); HRMS calcd for $\text{C}_{23}\text{H}_{23}\text{N}$: 313.1830, found: 313.1829.

1.2.3.2 Heck-Type Reactions with a Migrating Double Bond

Gerald Dyker

1.2.3.2.1 Introduction and Fundamental Instances

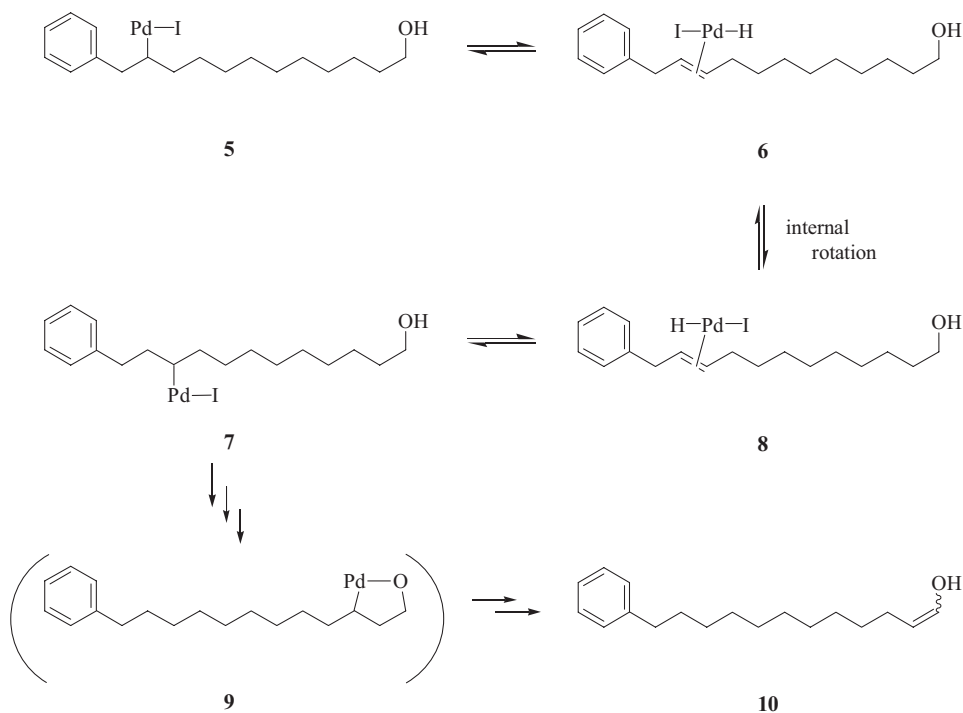
For the Heck reaction as discussed in Section III.2.1 the final position of the olefinic double bond of the products must not necessarily be the same as in the starting materials (for example Schemes 8, 9, and 10 of Section III.2.1) [1]. The selectivity is often driven by stereochemical requirements, because the β -hydrogen elimination step which forms the double bond proceeds exclusively in a syn manner (if a *trans* β -hydrogen is eliminated, one should suspect major deviations from the general mechanism of the Heck reaction, for example electrophilic substitution instead of carbopalladation). An impressive example of a double bond migration is depicted in Scheme 1 – instead of olefins the coupling reaction of iodobenzene **1** with the olefinic alcohol **2** results in the isomeric aldehydes **3** and **4** as final products [2]. Reactions of this type have emerged as valuable tools for the synthesis of carbonyl compounds and also as crucial steps in domino processes.



Scheme 1. aldehydes from a Heck-type reaction with an alcohol.

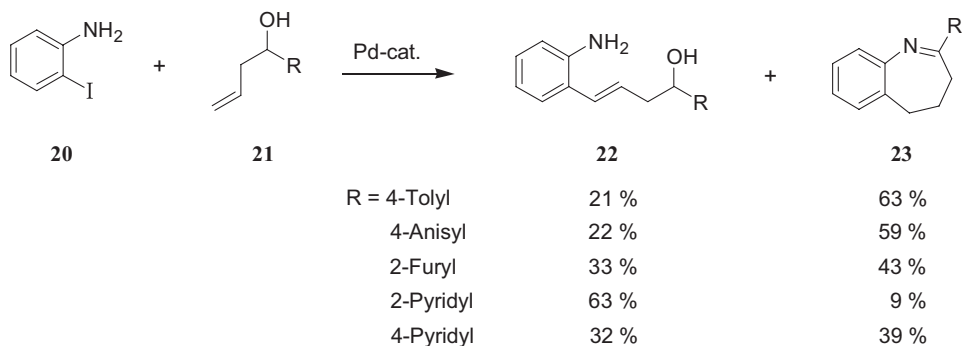
1.2.3.2.2 Mechanism

The example in Scheme 1 illustrates that migration of a double bond in Heck-type reactions can proceed even along an extended alkyl chain. Obviously the reversibility of β -hydrogen elimination is crucial for this process, enabling multiple β -hydrogen elimination/readdition sequences (Scheme 2): the main product of the initial carbopalladation **5** undergoes the first β -hydrogen elimination, either to the olefin complex **6** or to its regioisomer with the olefin in conjugation with the phenyl group. Because of the reversibility the latter regioisomer might react back to **5**. For productive readdition of the still coordinated hydrido palladium halide an internal rotation must first occur, resulting in π -complex **8** which leads to the σ -complex **7**. Repeating this sequence overall nine times gives the enol **10**, which, of course, tautomerizes to the thermodynamically favored aldehyde **3**. Also oxapalladacycles such as **9** should be taken into consideration – interaction between the metal center and the OH group seems to have some importance in the reaction, because with similar alkyl or silyl ethers migration of the double bond is suppressed.



Scheme 2. Possible intermediates in the migration of a double bond along a dodecyl chain.

alcohols, in particular, reveals that coordinating groups on the substrate can strongly interfere with double bond migration.



Scheme 5. Synthesis of benzazepines **23**.

Experimental

Benzocyclohept-2-ene-2-carboxaldehyde (**15**)

A mixture of 165 mg (500 μ mol) 1,2-diiodobenzene (**13**), 1.45 g (2.50 mmol) allylic alcohol (**14**), 400 mg (4 mmol) triethylamine, 5.6 mg (25 μ mol) of palladium acetate, and 10 mL dry DMF is stirred in a screw-capped tube at 80 °C for 44 h under nitrogen. After addition of 50 mL water the solution is extracted with diethyl ether (3 \times 30 mL). The combined organic layers are filtered through silica and concentrated in vacuo. By flash-chromatography (TLC: silica, diethyl ether–hexane 1:1; R_f = 0.60, 0.70) the product with R_f = 0.70 is isolated and distilled in vacuo (80 °C; 0.10 mbar) to give 70 mg (81 %) colorless crystals **15**, m.p. 73–76 °C. ^1H NMR (CDCl_3 , 500 MHz): δ = 2.73 (m, 2H), 3.05 (t, 2H), 3.72 (s, 2H), 6.56 (t, J = 1.0 Hz, 1H), 7.13–7.18 (m, 4H), 9.31 (s, 1H). ^{13}C NMR (CDCl_3 , 500 MHz): δ = 28.17 (t), 30.76 (t), 31.14 (t), 126.55, 127.04, 128.37, 128.57 (all d), 140.14, 140.42, 140.90 (all s), 153.84 (d), 194.22 (d). MS: m/z (%) = 172 (97) [M^+], 170 (27), 157 (24), 143 (79), 141 (49), 129 (73), 128 (100), 127 (24), 117 (66), 116 (95), 115 (80), 91 (29).

1.2.3.3 Enantioselective Olefin Isomerizations

Andrea Christiansen and Armin Börner

1.2.3.3.1 Introduction and Fundamental Examples

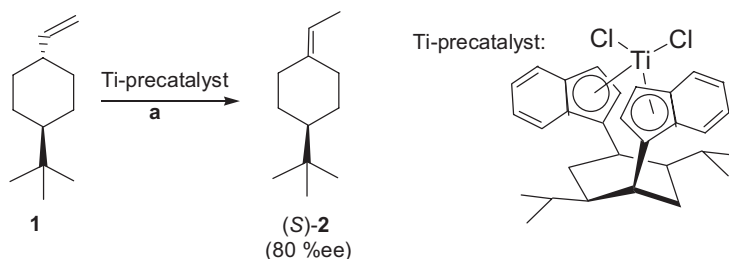
Enantioselective isomerization of olefins for preparation of optically active olefins has great synthetic potential with a long tradition [1] and the non-stereoselective version is probably the most intensively investigated reaction in transition metal catalysis [2]. In particular, stereoselective hydrogen migration in α -functionalized olefins, for example allyl alcohols and allylamines [3], affording optically active aldehydes, ketones and amines, is part of the standard repertoire of enantioselective

tive reactions [4]. In contrast to other enantioselective reactions, however, for example hydrogenations, the optical purity of the products has been disappointingly low for a long time. The usefulness of this transformation first became apparent in 1983 when it was used as part of the synthesis of (–)-menthol on a technical scale, one of the largest asymmetric syntheses in the world (Takasago process). Up to now, it seems that metal complexes based on Rh or Ni bearing chiral trivalent phosphorus ligands are the most efficient catalysts. Occasionally chiral bases can also be successfully used [5].

The conversion of higher substituted to less substituted olefins is not favored thermodynamically. This obstacle can be overcome when the newly formed C=C bond gains stabilization by conjugation with another double bond, e.g. C=O, or an aromatic unit, or by equilibration into a more stable product in a consecutive reaction. The E–Z geometry of the starting olefin may have a significant effect on the configuration and enantioselectivity in the product.

1.2.3.3.2 Enantioselective Isomerization of Unfunctionalized Olefins

There are few examples of isomerization of achiral unfunctionalized olefins into enantiomerically enriched olefins. The most successful is the transformation of *meso,trans*-4-*tert*-butyl-1-vinylcyclohexane (**1**) into the corresponding alkene (*S*)-**2** (Scheme 1) [6]. When a C₂-symmetric titanocene catalyst, which can easily be prepared in three steps from enantiopure starting material, is used in the presence of LiAlH₄ as activator the product is obtained in 80 % ee. The rate of the reaction and the optical purity of the product are highly dependent on reaction temperature. The lower enantiomeric purity obtained at higher temperatures is apparently because of racemization by equilibration of the product, a process which is promoted by longer reaction times.

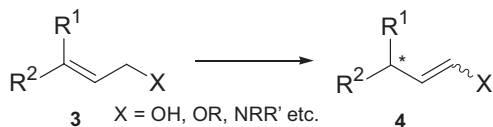


Scheme 1. Enantioselective isomerization of non-functionalized olefins: (a) catalyst generation: 2 % Ti-precatalyst, 8 % LiAlH₄, mesitylene, 164 °C; reaction performed at 23 °C, 67 h, sealed tube.

1.2.3.3.3 Enantioselective Isomerization of Allylamines, Allyl Alcohols and Allyl Ethers

Of substantial synthetic value for production of chiral fragrances and pharmaceutically useful intermediates is the isomerization of olefins of type **3** bearing oxygen functions and nitrogen-containing groups, respectively (Scheme 2). The terminal

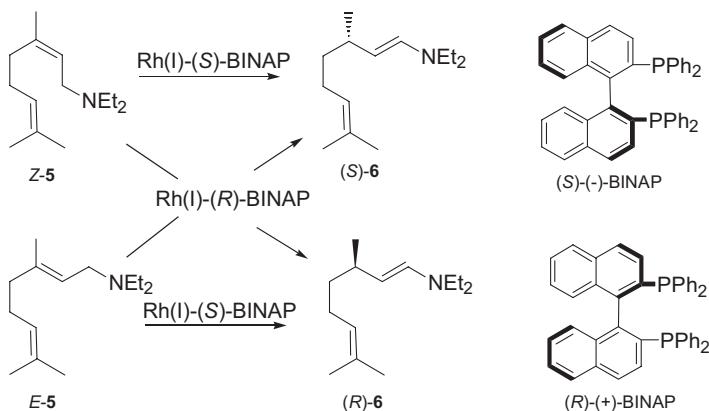
functionalities give rise to reactive products **4**, i.e. vinyl ethers, aldehydes, and enamines.



Scheme 2. Enantioselective isomerization of allyl compounds bearing oxygen or nitrogen containing groups.

1.2.3.3.4 Enantioselective Isomerization of Allylamines

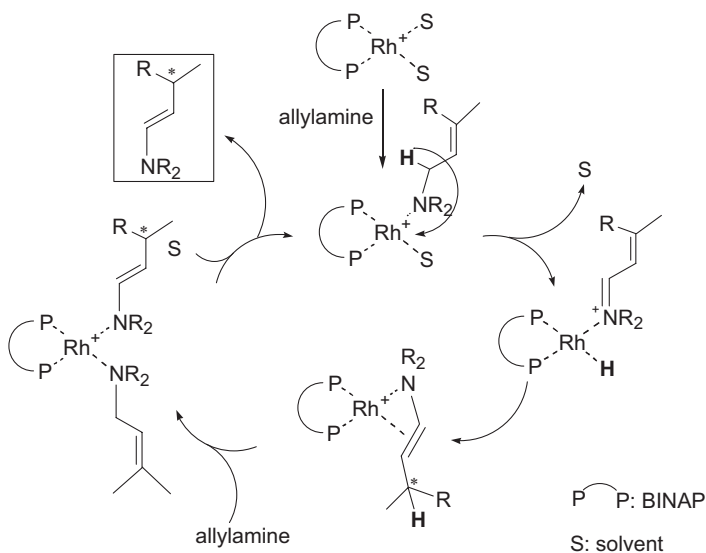
One of the most spectacular examples of a highly enantioselective isomerization is the reaction of allylamines with chiral Rh(I) catalyst based on the atropisomeric diphosphine BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) or related atropisomeric diphosphines as ligands [7]. Thus, reaction of neryldiethylamine (**Z-5**) with a Rh(I)–(*S*)-BINAP catalyst produces (*S*)-citronellal enamine [(*S*)-**6**] (Scheme 3). The geometry of the double bond in the product is perfect *E*. The undesired conjugated dienamine is formed only in traces, or is absent. By application of the enantiomeric ligand (*R*)-BINAP the enantiomeric enamine (*R*)-**6** is obtained. The latter can also be prepared by employing geranyldiethylamine (*E-5*) as starting material and application of the Rh(I)–(*S*)-BINAP catalyst.



Scheme 3. Correlation diagram between the stereochemistry of substrates, catalysts, and products for Rh(I)–BINAP-catalyzed enantioselective isomerization of allylamines. Reaction conditions: 2 mol% [Rh(BINAP)(COD)]ClO₄ (COD = 1,5-cyclooctadiene), H₂ (1 atm), THF, 40 °C, 23 h.

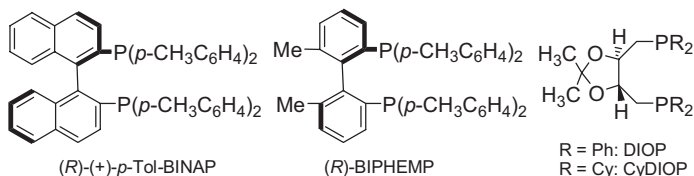
Use of the same substrate, with Rh(I)–(*R*)-BINAP yields enamine (*S*)-**6**. The exclusive formation of the (*E*) enamine in all reactions irrespective of the double-bond geometry of the substrate is remarkable. Every product in the scheme can be obtained with an enantioselectivity of more than 96 % ee.

Mechanistic studies of the isomerization of a prochiral allylamine with a Rh–diphosphine complex gave some evidence for a nitrogen-triggered mechanism in which the allylamine chelates to the metal center. The suggested mechanism, which was elaborated on the basis of a chiral Rh–BINAP catalyst, is depicted in Scheme 4 [8].



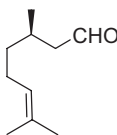
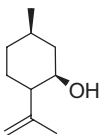
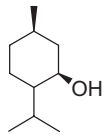
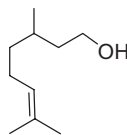
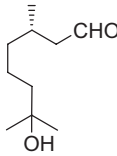
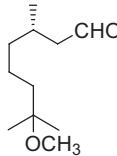
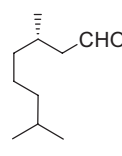
Scheme 4. A nitrogen-triggered mechanism for isomerization of allylamine with a Rh(I)–diphosphine catalyst.

The reaction is quite sensitive to the chiral ligand used. Diphosphines with an axially disymmetric biaryl moiety in the backbone give the best results. The effectiveness of *p*-Tol-BINAP as ligand, for example, is similar to that of BINAP. The related atropisomeric ligand BIPHEMP can also be used [9]. Among chiral aliphatic diphosphines tested, CyDIOP, which only differs from DIOP in the type of P-substituents, also gives satisfactory results.



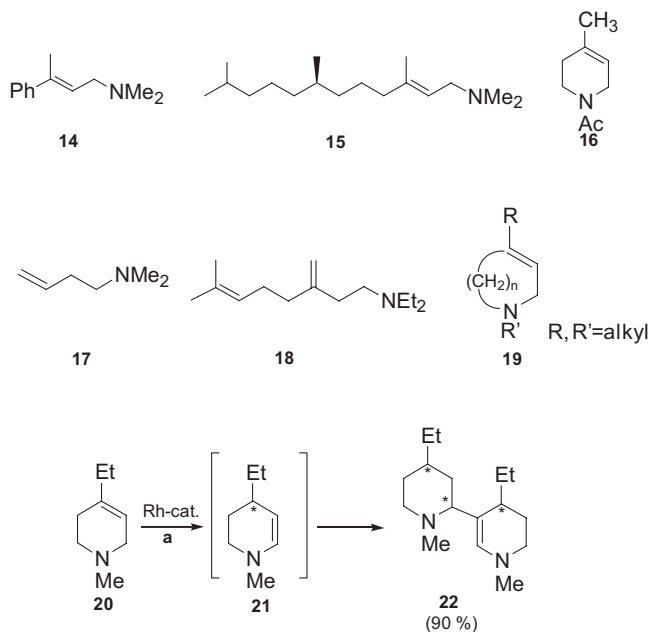
Enantiopure citronellal (**7**) which can be quantitatively derived by hydrolysis from citronellal enamine **6** can be used for the synthesis of a broad array of optically active natural products. A list of compounds produced commercially on a 7 to 1500 ton-scale annually, serving as fragrances, insect growth regulators, or intermediates in organic synthesis, is given in Table 1.

Table 1. Optically active terpenoids produced from allylamines by enantioselective isomerization.

			
7 (+)-Citronellal	8 (-)-Isopulegol	9 (-)-Menthol	10 (-) or (+)-Citronellol
			
11 (-)-7-Hydroxycitronellal	12 (S)-7-Methoxycitronellal	13 (S)-3,7-Dimethyl-1-octanal	

1.2.3.3.5 Scope and Limitations

The catalytic system is sensitive to traces of oxygen, moisture, and carbon dioxide. Also the conjugated diene–amine, which can be formed during the isomerization reaction as an undesired side-product may deactivate the catalyst. Excellent performance, even for industrial applications, can be achieved by application of a $[\text{Rh}(\text{BINAP})_2]^+$ catalyst at $>80^\circ\text{C}$, instead of the $[\text{Rh}(\text{BINAP})(\text{COD})]^+$ complex, which is preferentially used on laboratory-scale experiments at ambient temperature. Under these conditions the catalyst can be reused and the turnover number (TON) can be increased from 8000 to 400 000 TON, always under the precondition that careful pretreatment of the substrate and the reaction is undertaken. Because of its higher solubility, use of $[\text{Rh}(p\text{-TolBINAP})_2]^+$ facilitates reaction in organic solvents. The cationic catalysts ClO_4^- is preferentially used as counter-ion. In general, prochiral allylamines free from the geometrical isomer are required as starting materials. Remote hydroxy or methoxy groups in the side chain of the substrate do not affect the reaction. A styrene-derived allylamine, for example **14**, can be isomerized into the corresponding enamine with $>95\%$ ee by application of an $[\text{Rh}(\text{BINAP})_2]^+$ catalyst. Similarly, excellent enantioselectivity can be achieved with enamine **15**, a precursor of α -tocopherol (vitamin E), as substrate.



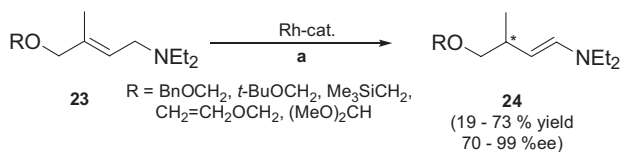
Scheme 5. Enantioselective isomerization of tetrahydropyridines and subsequent dimerization: (a) $\{\text{Rh}[(R)\text{-BINAP}](\text{COD})\}^+$, THF, 60–80 °C, 20 h.

For the isomerization, strongly basic amines are required as substrates. Allylamines bearing *N*-aryl groups retard the reaction. Allylamides are slow-reacting substrates and require a higher reaction temperature. Thus, *N*-acetyl-4-methyl-tetrahydropyridine (**16**) can only be subjected to isomerization at 150 °C. After a reaction time of 15 h the optically active enamide was obtained in 98 % ee.

Homoallylamines such as **17** or **18** cannot be isomerized, similarly to cyclic Z enamines of the general formula **19**.

Exceptionally tetrahydropyridine derivatives undergo isomerization, but the products cannot be isolated as monomers. Apparently in a subsequent thermal reaction diastereomeric dimers are formed, as depicted with enamine **20** as substrate (Scheme 5).

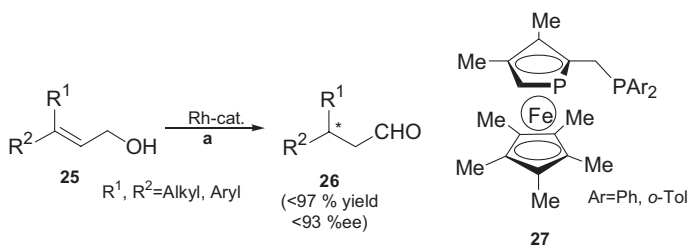
γ -Alkoxy-substituted allyldialkylamines **23** are cleanly isomerized to chiral enamines with a cationic BIPHEMP catalyst (Scheme 6) [9]. The exclusive regioselectivity toward formation of the enamine is remarkable. Enantioselectivities up to 99 % ee can be achieved. Different alkyl groups are tolerated. Replacement of the amino group by an amido functionality favors the isomerization in direction of the ether unit.



Scheme 6. Enantioselective isomerization of alkoxy-substituted enamines: (a) $\{\text{Rh}[(R)\text{-BIPHEMP}](\text{COD})\}\text{ClO}_4$, THF.

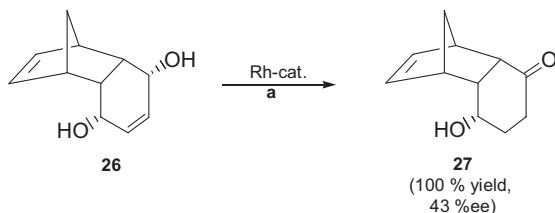
1.2.3.3.6 Enantioselective Isomerization of Allyl Alcohols

Similar to the reaction of allyl amines, allyl alcohols also undergo enantioselective isomerization in the presence of $[\text{Rh}(\text{BINAP})(\text{COD})]^+$ [10]. Yields and enantioselectivity are usually moderate, however. Considerable improvement was recently achieved by application of Rh(I) catalysts bearing phosphaferrrocenes, **27**, as chiral ligands (Scheme 7) [11]. These air-stable complexes, which can be recovered after the reaction, afford chiral aldehydes with up to 93 % ee.



Scheme 7. Chiral aldehydes produced by enantioselective isomerization of allyl alcohols with $[\text{Rh}(\text{phosphaferrrocene})(\text{COD})]^+$ catalysts, THF, 70–100 °C, 24 h.

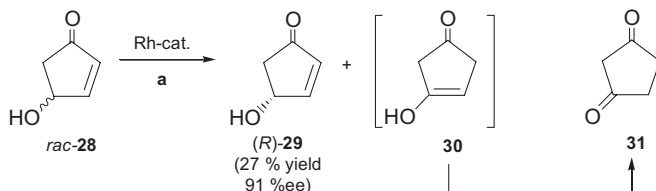
The meso-diene-diol **26** can be isomerized to the optically active alcohol **27** in quantitative yield and 43 % ee (Scheme 8) [12].



Scheme 8. Enantioselective isomerization of meso-enediols: (a) $\{\text{Rh}[(S)\text{-BINAP}](\text{COD})\}^+$, THF, 25 °C, 40 h.

Enantioselective isomerization can be advantageously used for the kinetic resolution of racemic allyl alcohols. For example treatment of 4-hydroxy-2-cyclopentenone (rac-**28**) in the presence of $\{\text{Rh}[(R)\text{-BINAP}](\text{MeOH})_2\}^+$ gives rise to the enantiomerically enriched allyl alcohol (*R*)-**29** (Scheme 9) [13]. This unsaturated hydroxy ketone is an important building block for the synthesis of prostaglandins

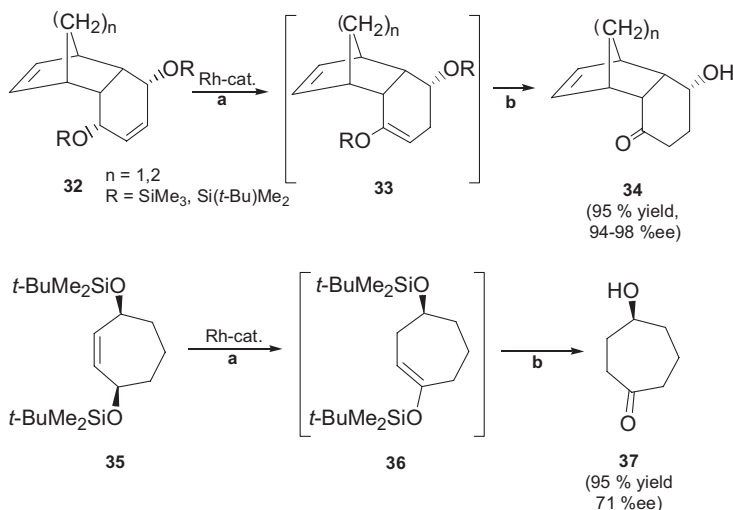
[14]. The opposite enantiomer of the starting material is selectively isomerized to enol **30** which tautomerizes to cyclopentane-1,3-dione (**31**).



Scheme 9. Kinetic resolution of racemic cyclic allyl alcohols:
(a) $\{\text{Rh}[(R)\text{-BINAP}](\text{MeOH})_2\}^+$, THF, 0 °C, 14 days.

1.2.3.3.7 Enantioselective Isomerization of Allyl Ethers

Good results have been achieved in the isomerization of meso-ene-dialkyl ethers and their O-silylated derivatives [12]. The allyl silyl ether **32** reacts in the presence of a Rh-BINAP catalyst to give the chiral enolsilyl ether **33** (Scheme 10). On treatment with fluoride, cyclic ketones **34** result in excellent yield and enantioselectivity.

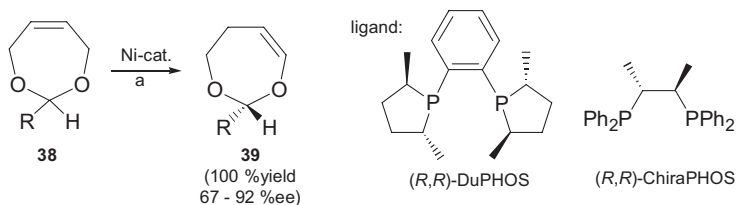


Scheme 10. Enantioselective isomerization of meso-endiol-bis-O-silyl ethers: (a) $\{\text{Rh}[(S)\text{-BINAP}](\text{COD})\}^+$, $\text{ClCH}_2\text{CH}_2\text{Cl}$, reflux; (b) Bu_4NF .

vity. The efficiency and enantioselectivity achieved are comparable with those of an enzymatic process. Interestingly, on application of the identical catalyst the direction of enantioselective isomerization is opposite when diol **26** is used.

Under these conditions cycloheptene derivative **35** also reacts [15]. After cleavage of the silyl ether, cyclic hydroxy ketone **37** can be isolated in 95% yield and 71% ee.

2-Substituted 5-methylene-1,3-dioxepines **38** are converted into vinyl acetals **39** by Ni catalysts bearing (*R,R*)-DuPHOS or (*R,R*)-ChiraPHOS as chiral ligands (Scheme 11) [16]. Similarly high enantioselectivity can be achieved with 5-methylene-1,3-dioxanes as substrates [17]. Chiral Ru-catalysts are less efficient [18]. Cyclic acetals obtained are an useful starting material for preparation of macrolide antibiotics and other polyketide-derived natural products.



Scheme 11. Enantioselective isomerization of 4,7-dihydro-1,3-dioxepines: (a) Ni(ligand) X_2 ($X = \text{Cl, Br, I}$, 5 mol%), 1.5 equiv. LiBHET₃, THF, or toluene, -55 to 20 °C, 2.5 to 72 h.

Experimental

(*S,E*)-Diethylcitronellenamine [(*S*)-**6**] [7]

A THF (5 mL) solution of {Rh[(*S*)-BINAP](COD)}ClO₄ (0.025 mmol) was treated with dihydrogen (1 atm at ambient temperature) for 15 min and excess dihydrogen was replaced by argon. To this catalyst solution neryldiethylamine **5** (0.52 g, 2.5 mmol) was added and the resulting scarlet–vermilion solution was heated at 40 °C for 23 h. The reaction was quenched by addition of excess diphos. After removal of the solvent, vacuum distillation of the residue using a Kugel–Rohr distillation apparatus gave (*S,E*)-*N,N*-diethyl-3,7-dimethyl-1,6-octadienylamine [(*E*)-diethylcitronellenamine] in over 96 % yield and >98 % ee. $[\alpha]_{\text{D}}^{20} = 77.6^\circ$.

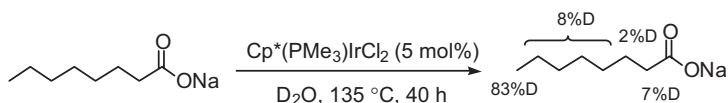
1.2.3.4 Palladium-catalyzed Deuteration

Seijiro Matsubara

Treatment of organometallic compounds with deuterium oxide normally affords regiospecific deuterium-labeled compounds. This quenching method is mainly used to confirm the presence of organometallic compounds in a reaction mixture. As a preparative method, base catalyzed H–D exchange of acidic protons and acid-catalyzed H–D exchange via cationic intermediates have already been reported [1–3]. In those cases, the former cannot be used for sp^3 C–H bond-formation without activation by a specific functional group such as a carbonyl group, and the latter is often accompanied by skeletal rearrangement. In contrast, transition metal catalyzed H–D exchange reactions based on C–H activation steps are also preparative methods for deuterium labeled compounds, and are not necessarily assisted by a specific functional group. Many sorts of transition metal catalyst have been reported for H–D exchange reactions. In transition metal-catalyzed reactions deuterium oxide,

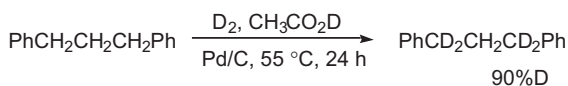
deuterium gas, and formic acid-D₂, and benzene-d₆ have usually been used as D source. Among these, deuterium oxide (D₂O) is the most attractive economically.

Since Anet and St. Jacques reported the H–D exchange reaction of cyclooctene with D₂O and Pd on charcoal in 1966 [4], several types of transition metal-catalyzed H–D exchange reaction of organic compounds with D₂O have been reported. As pioneering systematic studies, Ganet [5] and Shilov [6] showed that K₂PtCl₄ was an efficient catalyst for the H–D exchange reaction of arenes and alkanes with D₂O. In their methods they tried to use homogeneous phases as the reaction mixtures by use of additives such as inorganic acids. The level of deuteration was not always satisfactory. After this work, many metal catalysts, for example Rh, Co, Ru, Mn, Mo, and Pt were also shown to be effective for the H–D exchange reaction [7]. Bergman reported the iridium-catalyzed H–D exchange reaction on sp³ carbon with D₂O as shown in Scheme 1. The deuteration ratios were good and regioselectivity was also observed [8].



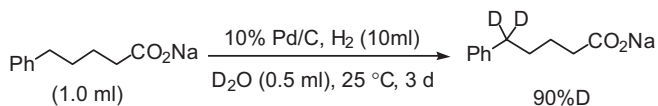
Scheme 1. H–D exchange of sodium octanoate with Cp^{*}(PMe₃)IrCl₂.

Heterogeneous palladium catalysts also have activity in the H–D exchange reaction. As shown in Scheme 2, an H–D exchange reaction was observed at the benzylic position with palladium on charcoal (Pd/C) under deuterium gas in the presence of CH₃CO₂D [9]. This combination of transition metal catalyst and deuterium gas has also been used for H–D exchange of a polymer, but the exchange ratio was quite low [10]. Considering the difficulty of handling, deuterium gas is not an appropriate D source. Deuterium oxide is much preferred because of its availability and ease of handling.



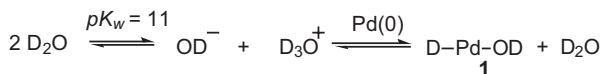
Scheme 2. H–D exchange at the benzylic position by D₂, Pd/C, and CH₃CO₂D.

The use of deuterium oxide as D source under the action of Pd/C ad catalyst is shown in Scheme 3. The catalyst was prepared from 10 % Pd on charcoal and H₂ gas and shown to be effective for H–D exchange on benzylic carbon [11a].



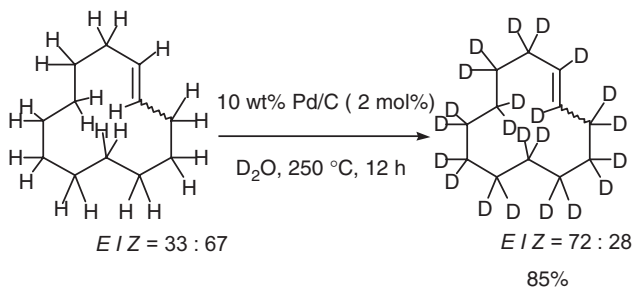
Scheme 3. H–D exchange reaction at the benzylic position with D₂O and premixed catalyst (10 % Pd/C and H₂).

When deuterium oxide is used as D source, the reaction temperature should be considered. When water in a closed pot is heated beyond the boiling point, it becomes subcritical and, eventually, supercritical [12]. Water under these conditions should also have potential in organic reactions [13, 14]. The same should happen with deuterium oxide. The value of pK_w for subcritical water should be noted. It has the low value of ca. 11 under typical hydrothermal conditions (250 °C/4–5 MPa). This means that hydrothermal deuterium oxide ionizes to a greater extent than under ambient conditions (1000 times more) and several acid-catalyzed reactions can actually be performed conveniently under supercritical or subcritical conditions without adding any acid. It is also interesting to perform transition metal-catalyzed reactions under hydrothermal conditions. Under these conditions, one should consider the redox equilibrium shown in Scheme 4 [15].



Scheme 4. Assumed oxidative insertion of Pd(0) into deuterium oxide under hydrothermal conditions.

Palladium deuteride **1** may act as an activator of C–H bonds at allylic positions and may form π -allyl palladium. Via the equilibrium between π -allyl palladium and alkene, H–D exchange will occur by C=C double bond migration. As shown in Scheme 5, cyclododecene was converted into the fully deuterated compound by treatment with hydrothermal deuterium oxide in the presence of Pd/C catalyst. Without Pd/C, no deuteration was observed under these reaction conditions [16].



Scheme 5. Treatment of cyclododecene with deuterium oxide and Pd/C under hydrothermal conditions.

Under the same conditions, several types of hydrocarbon are also converted to fully deuterated compounds. The results are summarized in Table 1. Cyclooctene was also transformed into fully deuterated cyclooctene without a skeletal rearrangement. As shown in entries 2 and 3, saturated hydrocarbons have also been transformed into fully deuterated compounds. As described above, an interaction between allylic C–H bonds and palladium hydride induces the H–D exchange reaction for alkenes. H–D exchange in alkanes, however, cannot be explained in this way. Direct C–H activation without assistance from any functional group may be a route to the formation of fully deuterated alkanes.

Table 1. Palladium-catalyzed deuteration of organic compounds under hydrothermal conditions.^a

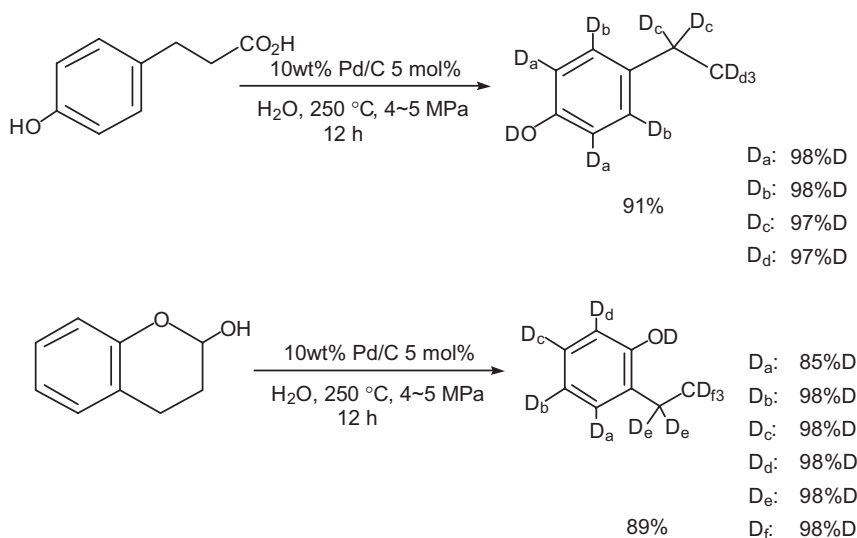
<div style="display: flex; align-items: center; justify-content: center;"> <div style="border: 1px solid black; padding: 2px 5px; margin-right: 10px;">Substrate (C_iH_mO_n)</div> <div style="text-align: center; margin-right: 10px;"> $\xrightarrow[\text{D}_2\text{O, 250 } ^\circ\text{C}]{10 \text{ wt\% Pd/C (2 mol\%)}}$ </div> <div style="border: 1px solid black; padding: 2px 5px; margin-left: 10px;">Fully Deuterated Substrate (C_iD_mO_n)</div> </div>				
Entry	Substrate	Time (h)	D (%)	Yield (%) ^b
1	Cyclooctene	4	>95	80
2	Cyclododecane	6	>95	84
3	Cyclopentadecane	4	>95	99
4	<i>n</i> -Pentadecane	16	76	98
5	Cyclooctanone	10	>95	86
6	Cyclodecanone	12	>95	83
7	Cyclododecanone	4	>95	87
8	Cyclopentadecanone	10	>95	99
9	2-Dodecanone	11	>95	93

^a Substrate (5.0 mmol), Pd/C (10 wt% palladium on carbon, 100 mg, 2 mol% Pd), and D₂O (20.0 g)

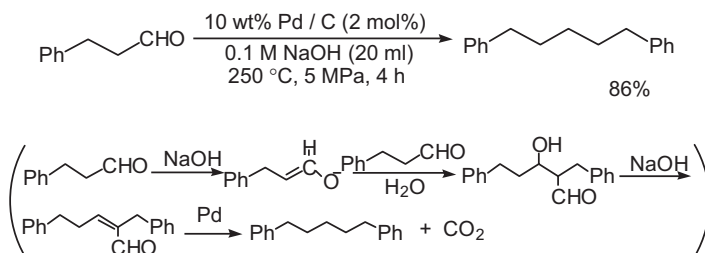
^b The yields were isolated yields.

Except for some activated acids, for example aryl carboxylic acids, decarboxylation of free carboxylic acids is often difficult [17]. Under the reaction conditions used for the deuteration in Scheme 6 (i.e. Pd/C catalyst, in deuterium oxide at 250 °C/4–5 MPa), decarboxylation was observed – a carboxyl group is exchanged with a D atom, accompanied by H–D exchange reaction on all carbons [18].

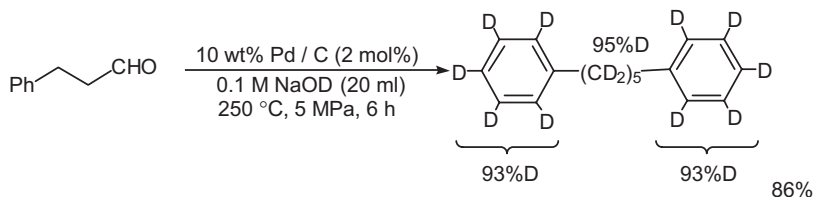
As shown in Scheme 7, treatment of hydrocinnamaldehyde with a catalytic amount of Pd/C in 0.1 M NaOH at 250 °C for 4–5 h gave the coupling product 1,5-diphenylpentane in 90 % yield [18]. The reaction pathway is supposed to be as follows. Aldol, which was formed by the aldol reaction under basic condition, was converted into enal. The enal was transformed into the product via reduction [19] and decarbonylation [18]. As shown in Scheme 8, this reaction can be used for preparation of the fully deuterated compound.



Scheme 6. Decarboxylative deuteration.



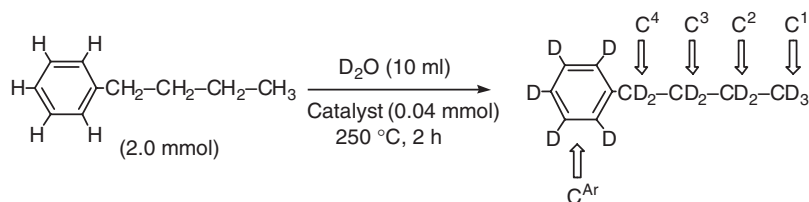
Scheme 7. Aldol condensation followed by Pd/C catalyzed degradation reaction.



Scheme 8. Deuteration by aldol condensation followed by Pd/C-catalyzed degradation reaction

Deuterated compounds have recently aroused interest not only for the laboratory use but also for practical application. Deuterium-labeled polymers are regarded as feasible materials for wave guides in optical communication, because of their transparency in the 500–800 nm infrared region [20]. For this purpose greater distribution of deuterium atoms on the polymer is preferable. The preparation of

deuterium-labeled polymers has been performed by a polymerization of labeled monomers. Direct H–D exchange has also been attempted occasionally. For example, active protons in a polymer, such as N–H in polyamides, are exchangeable with deuterium oxide [21]. Attempts have also been made to exchange C–H in hydrocarbon skeletons with D₂ gas in the presence of transition metal catalysts [22], but the exchange ratio was quite low. Hydrothermal transition metal-catalyzed deuteration is readily applicable to different types of compound, deuteration of polystyrene was examined. In this the efficiency on the benzene rings may have priority. The activity of metal salts as catalysts in the hydrothermal deuteration reaction in Scheme 9 are shown in Table 2 [23]. Among the catalysts listed use of Pd/C as catalyst was most efficient in H–D exchange on sp³ carbon. For exchange efficiency on benzene rings platinum(IV) oxide (PtO₂) gave better results.



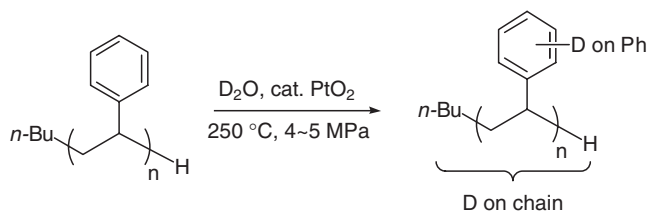
Scheme 9. H–D exchange reaction of butylbenzene.

Table 2. Metal salt-catalyzed deuteration of butylbenzene under hydrothermal conditions.^a

Run	Catalyst	C ^{Ar}	C ¹	C ²	C ³	C ⁴
1	Pd/C	20 %	67 %	42 %	49 %	43 %
2	PdO	2	61	38	50	42
3	PtO ₂	28	42	26	32	30
4	Pd black	<5	32	14	24	16
5	Raney Ni	3	28	10	13	5

^a Substrate (2.0 mmol), catalyst (2 mol% Metal), and D₂O (20.0 g).

As shown in Table 3, polystyrene samples were treated with hydrothermal deuterium oxide in the presence of a catalytic amount of PtO₂. The samples were commercially available from Aldrich as 800, 13 000, 44 000, and 280 000 Mw standards [23]. In the reaction using molecular weight 800, H–D exchange occurred on each carbon of the molecule. In the rather higher molecular weight samples in Table 3 the exchange efficiency decreased substantially on the carbon chain, but gently on the benzene rings. A tendency for selective exchange on benzene rings was observed in this PtO₂-catalyzed reaction.

Table 3. Deuteration of polystyrene with D₂O–PtO₂.

Aldrich Standard PS Mw	Reaction times (h)	D (%) on Ph	D (%) on Chain	Yield (%)
800	14	61	43	>99
	100	71	52	>99
13000	14	28	2	>99
	100	42	7	>99
44000	13	20	1	>99
	100	44	3	>99
280000	13	22	<1	>99
	100	38	2	>99

The palladium catalyzed H–D exchange reaction have been examined for 40 years, since Anet et al. reported their preliminary results. For H–D exchange at the benzylic position, combination of a Pd catalyst and a deuterium source, for example D₂ or D₂O works well at ambient temperature. At higher temperature, H–D exchange is even observed on sp³ carbon. Beyond 200 °C in D₂O (hydrothermal conditions) H–D exchange would occur at any carbon. Although hydrothermal conditions mean the reaction is performed at 200–250 °C and 3–5 MPa, the surrounding water (or D₂O) also prevents decomposition of organic compounds. It is different from direct heating. The structure of D₂O under hydrothermal conditions is important information for understanding the H–D exchange reaction. At the same time, the redox equilibrium between the transition metal catalyst and D₂O under hydrothermal conditions will be more important. Both of them have not been studied well. Reactions under hydrothermal conditions should be regarded as very useful not only for H–D exchange but also for organic syntheses in general.

Experimental

Decarboxylation and Decarbonylation Procedure (Scheme 6) [18]

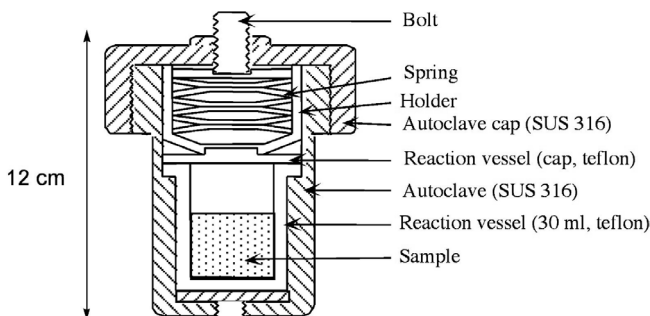


Figure 1. 30 mL teflon-lined autoclave.

The vessel is designed to release the internal overpressure [16]. It is commercially available from Shikokurika (Kochi, Japan). A Teflon vessel containing a mixture of 10 wt% Pd on active carbon (100 mg, 0.1 mmol Pd), deuterium oxide (20 mL), and the carbonyl compound (carboxylic acid, aldehyde, lactone, or amide, 2.0 mmol) was placed in an autoclave and sealed. The autoclave was placed in an oven at 250 °C. After heating for 12 h it was cooled to room temperature and the reaction mixture was extracted with pentane and ether. Because the Teflon vessel partially absorbs organic compounds, it was washed with hexane and water, for 30 min each, using an ultrasonic cleaner, to extract the product completely. The solvents used for washing were extracted with ether. The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. The product obtained was purified by short-column silica-gel chromatography. Instead of the vessel in Fig. 1, a glass sealed tube can be used. If a sealed tube is used, however, care should be taken to protect against the possible consequences of explosion, because the internal pressure is quite high.

1.2.4

Copper- and Palladium-catalyzed Allylic Acyloxylation

Jean-Cédric Frison, Julien Legros, and Carsten Bolm

1.2.4.1 Introduction

Allylic acetates and, more generally, allylic carboxylates, are important intermediates in organic synthesis. Indeed, the acetoxy moiety is an excellent leaving group that can be easily replaced by various nucleophiles [1]. Direct introduction of oxygen functionality on the allylic position by radical-initiated reactions [2] and selenium- [3] and transition metal-mediated [4] reactions has already been reported. Because of the increasing demand for efficient and economic processes, however, the use of allylic oxidation promoters which can be used in catalytic amounts is of great interest. Among these, copper- [5] and palladium catalysts [6] are among the most efficient for selective allylic acyloxylation reactions.

1.2.4.2 Copper-catalyzed Allylic Acyloxylation

1.2.4.2.1 General Considerations

The copper-catalyzed allylic acyloxylation of alkenes, referred to as the Kharasch–Sosnovski reaction is a highly valuable transformation. The combination of *tert*-butyl perbenzoate and catalytic amounts of copper bromide in benzene under reflux enables the selective conversion of alkenes into the corresponding allyl esters [5, 7]. The reaction is highly chemoselective and works particularly well with cyclic olefins. For example, oxidation of cyclohexene under the abovementioned conditions delivers the corresponding cyclohex-1-en-3-yl benzoate in 70 % yield. Oxidation of acyclic olefins usually proceeds with a high regioselectivity. Secondary allylic esters are formed preferentially (Table 1, entries 2–5) [8]. As a consequence, the same allylic ester is obtained in reactions starting from allyl benzene and β -methylstyrene (Table 1, entries 3 and 4) [8]. The regioselectivity is somewhat dependent on the reaction conditions, e.g. the oxidant, the copper source or the solvent. Some substrates with benzylic substituents, for example toluene, react only sluggishly, because formation of the allyl intermediate requires loss of the aromaticity [9]. Other compounds with multiple bonds also react, and the allylic oxidations of allenes and alkynes have also been reported (Table 1, entries 5 and 6) [10]. Substrates with electron-rich heteroatoms can be oxidized under these conditions (Table 1, entry 7). For example, ethers give the corresponding carboxylate acetals in good yields [11]. The most commonly used solvents for the reaction are benzene, acetone, and acetonitrile.

The main limitations of copper-catalyzed allylic acyloxylation are the long reaction times, the need for high temperatures, and the use of excess olefin, the yield often being calculated on the basis of the perester.


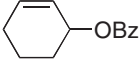
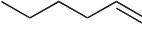
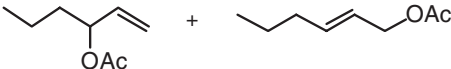
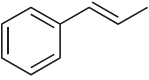
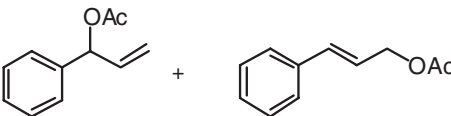
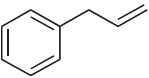
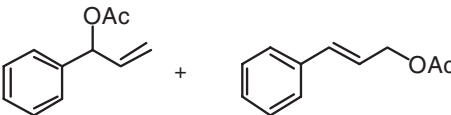

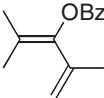
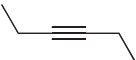
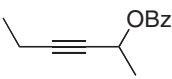

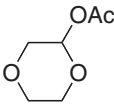
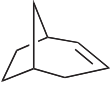
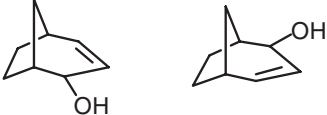
For these reasons, recent investigations have focused on the development of more practical reaction conditions. Bases such as DBU or DBN increase the reaction rate, and the reaction can be performed at room temperature within a few hours in the presence of these additives [12]. The combination of $\text{Cu}(\text{CH}_3\text{CN})_4\text{BF}_4$ as catalyst and benzonitrile as solvent enables the reaction to be conducted without excess olefin in good yields and short reaction times [13]. Recyclable catalysts have also been developed. Fluorous [14] or water-soluble catalysts [15] and Cu-exchange zeolites [16] can be reused and enable several catalytic cycles without loss of activity.

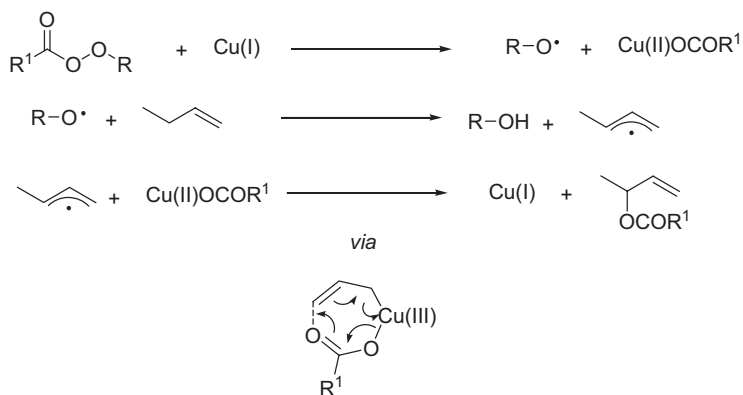
1.2.4.2.2 Mechanism

The generally accepted mechanism of the Kharasch–Sosnovski reaction is shown in Scheme 1. It is initiated by reductive cleavage of the perester by the copper salt [8] generating a copper(II) carboxylate and a *tert*-butoxy radical. The latter reacts with the olefin giving an allyl radical that is in turn trapped by the copper(II) carboxylate. Subsequent coupling of the ligands affords the product and regenerates the catalyst. This last step has been controversial, and the regioselectivity observed in transformations of acyclic olefins has been useful for understanding the mech-

anism [9]. The preferential formation of the secondary allyl ester is explained by a pericyclic rearrangement proceeding via a seven-membered transition state, in which the allyl fragment is coordinated to copper by its less substituted side.

Table 1. Selected examples of the substrates used in copper-catalyzed acyloxylation.

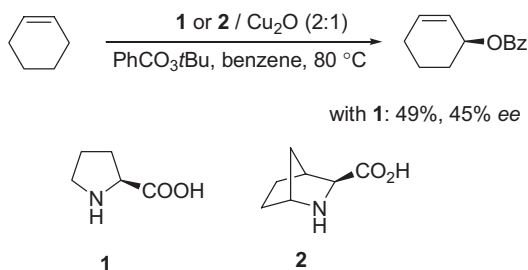
Entry	Substrate	Product	Yield (%)
1			70
2		 >90 : < 10	90
3		 71 : 29	40–45
4		 100 : 0	45–50
5			47
6			74
7			73
8		 1 : 1	57 (after hydrolysis)



Scheme 1. Mechanism of copper-catalyzed allylic acyloxylation.

1.2.4.2.3 Enantioselective Allylic Acyloxylation

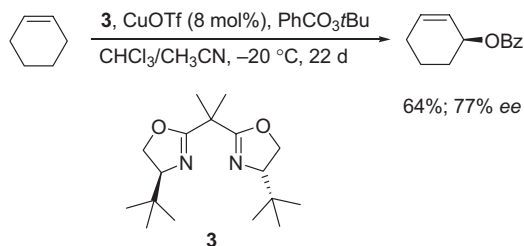
Although the first example of an asymmetric Kharasch–Sosnovski reaction with a chiral perester was reported as early as 1965 [17], major advances have only been made in the last ten years. In the early 1990s, Muzart carefully reinvestigated earlier results obtained by Araki and Nagase [18]. After intensive optimization of the reaction conditions, the acyloxylation of cyclopentene and cyclohexene gave products with up to 59 and 45 % ee, respectively. The best conditions for the oxidation of cyclohexene were found to involve the use of 5 mol% copper oxide, 10 mol% proline (**1**), and *tert*-butyl perbenzoate/benzoic acid in benzene under reflux (Scheme 2) [19].



Scheme 2. Proline as chiral inductor in the copper-catalyzed allylic oxidation.

Finally, the best enantioselectivity with this system was obtained by using copper(II) acetate, with propionic acid as additive, and by conducting the reaction at lower temperatures (70 %, 57 % ee) [20]. Later, the use of an azanorbornane acid, which was a bicyclic analog of proline, resulted in better activity and enantioselectivity (65 % ee) [21]. In the same year, Pfaltz reported the use of chiral bisoxazoline **3** in the enantioselective copper-catalyzed acyloxylation reaction (Scheme 3) [22]. Although long reaction times were required, the enantioselectivity achieved with

the corresponding copper complexes were better than those obtained with the proline catalyst. For example, in the presence of 6–8 mol% copper catalyst and with *tert*-butyl perbenzoate as oxidant, cyclohexene was obtained with 77 % ee (64 % yield) after 22 days at -20°C . Use of cyclopentene (and cycloheptene, a difficult substrate) resulted in slightly better enantioselectivity with 84 % ee (61 % yield) and 82 % ee (44 % yield), respectively. Acyclic terminal olefins were also transformed, although with significantly lower yields and enantioselectivity (up to 36 % ee).



Scheme 3. C_2 -symmetric bisoxazoline **3** in allylic oxidation according to Pfaltz.

Further improvement of the enantioselectivity was achieved by modifying the solvent and the oxazoline (43 %, 80 % ee in acetonitrile) [23]. The high enantioselectivity was, however, accompanied by low conversions. This issue was addressed by Andrus, who employed electron-deficient peresters as oxidant. By weakening the O–O bond, it was assumed that the reaction rate could be increased [24]. In fact, with *tert*-butyl-*p*-nitro-perbenzoate, oxidation of cyclopentene could be performed, giving a product with 99 % ee, albeit at low conversion (41 % after 8 days).

After the initial successful application of C_2 -symmetric bisoxazolines, other oxazoline-based ligands were also employed. Andrus developed biaryl bisoxazolines **4** with both axial and central chirality [25]. Compared to the C_2 -symmetric bisoxazolines, however, these ligands were less successful in the oxidation of simple cyclic olefins (for cyclopentene: 78 % yield, 73 % ee at -20°C with *tert*-butyl-*p*-nitrobenzoate).

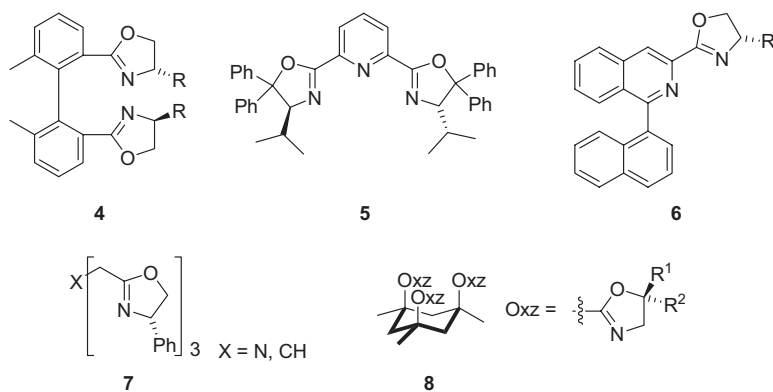


Figure 1. Other oxazolines employed in combination with copper salts in the asymmetric Kharasch–Sosnovski reaction

Singh applied pyridyl bisoxazoline (PYBOX) **5** and found that the oxidation proceeded with high enantioselectivity [26]. The innovation in this procedure was the preparation of the catalyst. Singh employed a slight excess of phenylhydrazine to reduce the Cu(II) complex to the active Cu(I) species, thereby dramatically improving catalyst activity. Cyclooctene was converted to the corresponding allylic ester with 81 % ee in 26 % yield after 24 h. The same reaction without phenylhydrazine gave a similar yield and enantioselectivity but required 30 days. Quinazoline- and quinoline-oxazoline ligands **6** led to lower enantioselectivity (64 % ee at best in the oxidation of cyclohexene) [27]. C₃-Symmetric trisoxazolines **7** bridged by a nitrogen or a carbon atom have been used by Katsuki [28]. Cyclopentene gave the corresponding product with 83 % ee in 81 % yield (at 0 °C) and with 93 % ee in 30 % yield (at –20 °C). Other more complex substrates are also oxidized with good enantioselectivity. Trisoxazoline **8** developed by Bolm was not as efficient in this reaction (29 % yield, 49 % ee) [29].

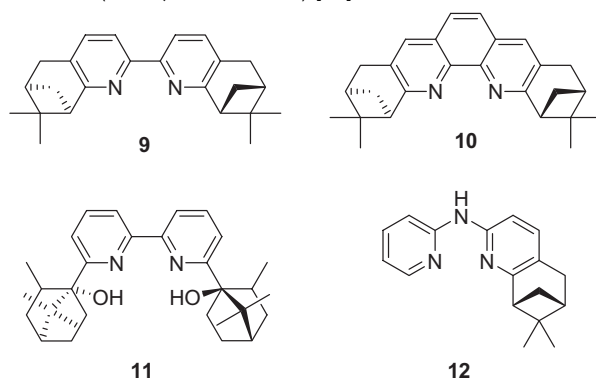


Figure 2. Pyridine derivatives for the enantioselective copper-catalyzed allylic oxidation.

Finally, pyridine derivatives have been used in the Kharasch–Sosnovski reaction. The combination of these ligands with copper salts led to significant acceleration of the rate of the reaction. After 30 min at room temperature, oxidation of cyclopentene with Cu(OTf)₂ and **9** gave the corresponding allylic esters with 48 % ee in 85 % yield (80 % yield and 59 % ee at 0 °C after 12 h) [30]. Use of the analogous phenanthroline **10** gave a product with 57 % ee in 86 % yield after a similar reaction time [31]. Bipyridine **11** gave better results (88 % yield, 61 % ee) albeit after longer times [32]. More recently chiral 2,2'-dipyridylamine **12** has also been employed, giving the product in high chemical yields but low enantioselectivity (17 % ee at best) [33].

1.2.4.3 Palladium-catalyzed Allylic Acyloxylation

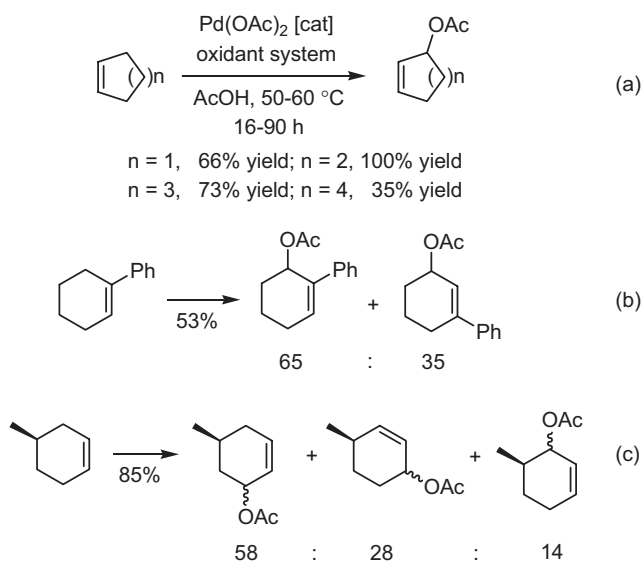
1.2.4.3.1 General Considerations

In the presence of alkenes, palladium(II) salts form Pd(II)–olefin complexes. For olefins with allylic hydrogen atoms, these complexes undergo a rapid rearrangement to π -allyl complexes by a process called allylic C–H activation [34]. Nucleo-

philic attack on the allyl moiety of a (π -allyl)palladium then leads to an allylically substituted olefin. This transformation, however, ultimately generates a Pd(0) complex, whereas Pd(II) is required for formation of the π -allyl complex. Thus, addition of a stoichiometric amount of an oxidant is essential for performing the reaction catalytically. Early processes involved CuCl_2 or nitric acid [35] but use of benzoquinone (BQ) or electron-transfer mediators led to more selective reactions which were applicable to a wider range of substrates [36]. Benzoquinone can also be used in catalytic quantities in the presence of co-oxidants such as peroxides [37] or molecular oxygen activated by metal macrocycles [38]. Palladium dimers or clusters are applicable with air or molecular oxygen as stoichiometric oxidants [39]. These later approaches are highly interesting for large-scale applications as water is the only effluent of the reaction.

1.2.4.3.2 Palladium-catalyzed Allylic Acyloxylation of Alkenes

Allylic acyloxylation of cycloalkenes are easily performed using the palladium/BQ-based process with a stoichiometric oxidant such as MnO_2 [36b], or O_2 activated by a metal catalyst [38] or a heteropolyacid [40]. Very good results are obtained for cycloolefins, especially 5-, 6- and 7-membered rings (up to 100% yield of the allylic acetoxylation products at 50–60 °C in acetic acid) whereas larger rings require extended reaction times and yields decrease significantly (Scheme 4a) [36, 38, 40]. Substituted cycloalkenes are also efficiently transformed but isomeric products are formed [36c]. This latter point is highly dependent on the nature and position of the substituent. For example, oxidation of 1-phenylcyclo-



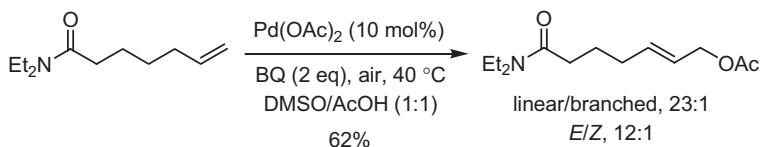
Scheme 4. Allylic acetoxylation of unsubstituted cycloalkenes (a), 1-phenylcyclohexene (b), and 4-methylcyclohexene (c).

hexene yields two isomeric allylic acetates (Scheme 4b). With 4-methylcyclohexene, the reaction is not selective, leading to three regioisomers each being formed as diastereomers (Scheme 4c).

Under forced reaction conditions, allylic acyloxylation products can undergo a second allylic oxidation [36]. Thus, 1,4-diacetoxycyclohexene can be obtained directly from cyclohexene in a reaction in which the main product is, however, the monoallylic acetate.

The asymmetric allylic acetoxylation of cycloalkenes has also been reported. In this case, the catalyst is a bimetallic palladium(II) complex bearing a chiral bisoxazoline or a chiral diphosphine (DIOP). The reaction is performed in acetic acid/sodium acetate under oxygen atmosphere at room temperature. Under these conditions, acetoxylation products of cyclohexene and cyclopentene are obtained with 55 % and 78 % ee, respectively, albeit in low yields [39a].

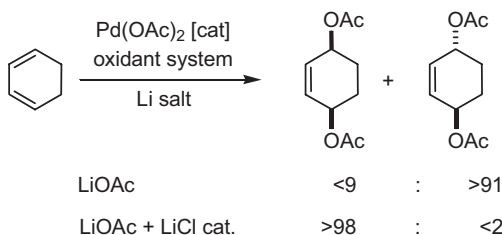
The conditions for allylic acyloxylation of internal olefins are, for reasons which are not clear, unsuitable for terminal olefins. They undergo Wacker oxidation (Markovnikov oxypalladation/ β -hydride elimination) to yield mixtures of vinyl acetates and methyl ketones [37a]. A combination of $\text{Pd}(\text{OAc})_2/\text{BQ}$ with air as co-oxidant in a mixture of DMSO/AcOH (1:1) enables conversion of a broad range of functionalized terminal olefins to the corresponding linear allylic acetates in acceptable yields (Scheme 5) [41].



Scheme 5. Allylic oxidation of a terminal olefin to the corresponding allylic acetates.

1.2.4.3.3 Palladium-catalyzed Allylic Acyloxylation of 1,3-Dienes

The allylic oxidation of 1,3-dienes catalyzed by Pd(II) complexes in the presence of BQ (added in stoichiometric quantities or used catalytically with a stoichiometric amount of a co-oxidant) leads to the formation of 1,4-oxidation products under mild reaction conditions (at room temperature in AcOH) [42]. A very interesting stereochemical aspect arises in 1,4-diacyloxylation reactions of cycloalkenes when carboxylate salts are used as nucleophiles. Although the relative stereochemistry



Scheme 6. Stereoselectivity in the diacetoxylation of 1,3-cyclohexadiene.

of the product is somewhat substrate-dependant, and the ring size and the position of the substituents have a large influence [42], high diastereoselective control can often be achieved. Thus, in the absence of chloride ions predominantly trans products are formed whereas on addition of catalytic amounts of chloride ions cis products are obtained (Scheme 6) [42]. When a chiral quinone derivative was used under chloride-free conditions the trans diacetoxo product of 2-phenyl-1,3-cyclohexadiene was formed with 45 % ee [43].

Interestingly, performing the reaction with 1,4-cyclohexadiene as substrate in the presence of a stoichiometric amount of LiCl affords *cis*-1-monoacetoxo-4-chlorocyclohex-2-ene in high yield [44]. Because chloride is more prone to substitution than acetate, it can subsequently be selectively exchanged by a nucleophile.

Experimental

General Procedure for Copper-catalyzed Enantioselective Synthesis of Cyclohex-1-en-3-yl Benzoate (Based on Refs. [26], [30], and [33])

A solution of $\text{Cu}(\text{OTf})_2$ (18 mg, 0.05 mmol) and the ligand (0.06 mmol) in degassed acetone (4 mL) is stirred under argon at room temperature for 1 h. Phenylhydrazine (0.06 mmol) is then added, and the mixture is stirred for 15 min. During this time, the color of the solution changes from blue–green to red, an indication of the reduction of Cu(II) to Cu(I). Cyclohexene (10 mmol, 1 mL) is added followed by dropwise addition of *tert*-butyl perbenzoate (190 μL , 1 mmol). During this time the color of the solution changes from red to blue–green. The reaction mixture is stirred at room temperature until the transformation is complete (disappearance of *tert*-butyl perbenzoate, monitored by TLC using SiO_2 plates and hexane–ethyl acetate 9:1). Acetone is then removed under reduced pressure and the remaining crude product is dissolved in CH_2Cl_2 (10 mL). The solution is washed with NaHCO_3 , brine and dried over Na_2SO_4 . Cyclohex-1-en-3-yl benzoate is obtained as a colorless oil after flash chromatography (silica gel with hexane–ethyl acetate (10:1) as eluent). ^1H NMR (CDCl_3 , 400 MHz): δ = 1.60–1.75 (m, 1H), 1.73–2.12 (ms, 5H), 5.46 (m, 1H), 5.78 (m, 1H), 5.96 (m, 1H), 7.37 (dd, J = 8.4, 7.4 Hz, 2H), 7.49 (m, 1H), 8.01 (dd, J = 8.4, 1.4 Hz, 2H). The enantiomer ratio was determined by HPLC using a chiral column (Chiralpak AD, heptane–isopropanol (99.6:0.4), flow rate 1 mL min^{-1} , t_R = 12.6 min, t_S = 13.8 min or Chiralcel OD-H, heptane–isopropanol (99.5:0.5), flow rate 0.5 mL min^{-1} , t_R = 17.8 min, t_S = 19.1 min).

Palladium-catalyzed Synthesis of 2-Cyclohepten-1-yl Acetate [36b]

$\text{Pd}(\text{OAc})_2$ (1.12 g, 0.005 mol), benzoquinone (2.16 g, 0.02 mol), MnO_2 (10.44 g, 0.12 mol), and anhydrous AcOH (250 mL) are placed in a 1-L round-bottomed flask equipped with a reflux condenser and a magnetic stirring bar. This heterogeneous mixture is equilibrated by efficient stirring for 30–60 min. Cycloheptene (9.61 g, 0.1 mol) is added, and the stirring is continued at 60°C for 28 h. After cooling of the solution to room temperature, pentane–ether (1:1, 250 mL) is added

and the reaction mixture is stirred for another 30 min. The two-phase mixture is filtered with suction through a Buchner funnel containing a layer (5–10 mm) of Celite. The Celite layer is washed successively with pentane–ether (1:1, 250 mL), water (250 mL), pentane–ether (1:1, 100 mL), and water (250 mL). After the organic phases have separated, the aqueous phase is extracted three times with pentane–ether (1:1, 250 mL). The combined organic phases are washed successively with water (250 mL), aq. NaOH (2 M; 250 mL and then 100 mL), water (250 mL), and finally dried over anhydrous MgSO_4 . After evaporation of the solvent, the product is purified by distillation to give 2-cyclohepten-1-yl acetate (11.25 g, 73 %), b.p. 61–62 °C (5 mm). ^1H NMR (200 MHz, CDCl_3): δ = 1.30–2.30 (m, 8H), 2.05 (s, 3H), 5.40 (m, 1H), 5.65 (m, 1H), 5.82 (m, 1H).

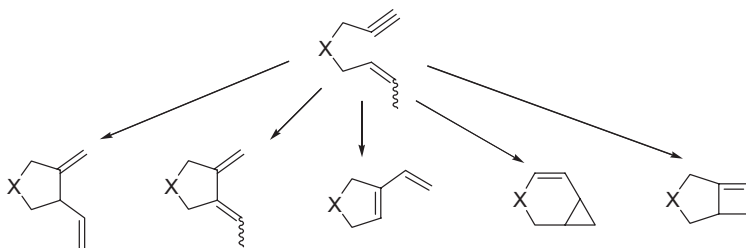
1.2.5

Transition Metal-catalyzed En-yne Cyclization

Minsheng He, Aiwen Lei, and Xumu Zhang

1.2.5.1 Introduction and Fundamental Examples

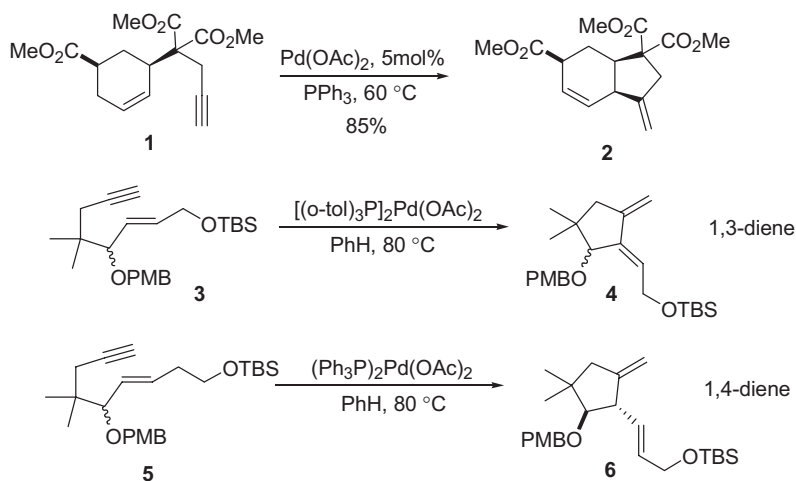
The increasing demand for development of efficient methods for preparation of various types of cyclic compound has motivated the organic community to pursue catalytic and atom-economic processes in the last few decades [1]. Toward this ideal, homogeneous transition metal-catalyzed cyclizations have been developed, with much success [2]. Among these, enyne cycloisomerizations such as Alder–ene reaction are particularly interesting and have been reviewed extensively [3–5]. Mechanistically, the Alder–ene reaction is related to the Diels–Alder cycloaddition, because both are concerted six-electron pericyclic reactions resulting in the formation of two σ -bonds [6]. Traditionally, the Alder–ene reaction is performed thermally and has very limited applications in organic synthesis. Recently, progress in transition metal-catalyzed cyclization resulted in great success in the field of carbocyclic and heterocyclic compound syntheses in a very mild and selective manner. The final outcome of the reaction depends on the catalytic systems and conditions employed (Scheme 1) [4, 7–10]. This chapter will focus upon the subset of transition metal-catalyzed intramolecular carbon–carbon forming reactions which generate one or more ring systems with concomitant loss of one or more unsaturated units and quantitative atom economy (ene-type reaction), i.e. cycloisomerization.



Scheme 1. Enyne cyclization.

The intramolecular Alder–ene reaction (enyne cycloisomerization reaction) with alkynes as the enophiles has found wide application compared with diene systems. The reason may be the ready chemo-differentiation between alkene and alkyne functionality and the more reactive alkyne moiety. Furthermore, the diene nature of the products will promote further applications such as Diels–Alder reactions in organic synthesis. Over the past two decades the transition metal-catalyzed Alder–ene cycloisomerization of 1,*n*-enynes (typically *n* = 6, 7) has emerged as a very powerful method for constructing complicated carbo- or heterocyclic frameworks. The transition metals for this transformation include Pd, Pt, Co, Ru, Ni–Cr, and Rh. Lewis acid-promoted cycloisomerization of activated enynes has also been reported [11].

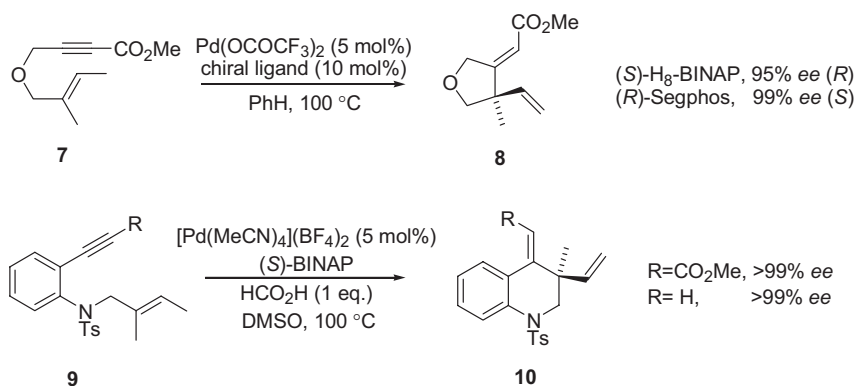
B.M. Trost is the pioneer in transition metal-catalyzed cycloisomerizations, particularly in developing Pd and Ru precatalysts and applying them in natural product syntheses. In one of his earliest works he reported that enyne **1** failed to transform under harsh thermal conditions (>550 °C), but it does successfully convert to 1,4-diene **2** with Pd(OAc)₂ under mild conditions (Scheme 2) [12]. The transition metal-catalyzed reaction also offers the possibility of generating either 1,3-dienes or 1,4-dienes as the products. It was found that the oxygen substitution may effect on regioselectivity (Scheme 2) [13]. Both Pd(OAc)₂ and [(PAr₃)₂Pd(OAc)₂] were found to be effective as catalysts. In addition, Trost introduced palladacyclopentadiene as the precatalyst and the reaction can be performed smoothly at 60 °C [14]. A rearrangement product and the [4 + 2] product was, however, found in the presence of DMAD; this can be regarded as the very first example of a 1,6-enyne metathesis reaction [15].



Scheme 2. Pd(II)-catalyzed Alder–ene reaction.

An asymmetric procedure was reported by Trost in 1989 [16]. The combination of [Pd₂(dba)₃]CHCl₃, a chiral carbocyclic acid such as Mosher's acid, and (*S*)-binaphthoic acid resulted in low but promising induction (33 % ee). Enantioselective

tivity was improved by introduction of the amidodiphosphane ligand and moderate ee was achieved. The carboxylic acid unit of the substrate is essential for high enantioselectivity. More efficient ligands such as (*S,S*)-(*R,R*)-trap, which was introduced by Ito and co-workers, gave an 1,4-diene as the major product with 95 % ee [17]. It was reasoned that the high enantioselectivity arose because of *trans*-coordination of the chiral phosphine, because *cis*-coordinating ligands (chiraphos and diop) reduce the ee to 6–15 %. In addition, this system seems to be very substrate-dependent (34–76 % ee for other examples).



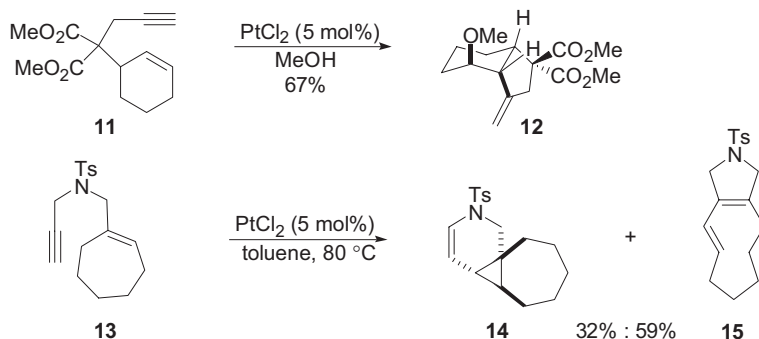
Scheme 3. Pd-catalyzed asymmetric cycloisomerization with *cis*-bidentate ligands.

Mikami et al. recently found that the cycloisomerization of 1,6-enyne **7** resulted in 84 % ee with typical palladium catalysts ($\text{Pd}(\text{OAc})_2$, $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3/\text{AcOH}$, $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3/\text{F}_3\text{CCO}_2\text{H}$), and BINAP [18]. To avoid the formation of the 1,3-diene, a methyl substituent was used to mask the vinyl hydrogen. Enantioselectivity and conversion were enhanced greatly by switching to $\text{Pd}(\text{OCOCF}_3)_2$ and H_8 -BINAP or Segphos systems, which resulted in up to 99 % enantiomeric excess (Scheme 3). They also extended this method to asymmetric cycloisomerization of 1,7-enynes to produce six-membered rings. Six-membered rings are usually regarded as more difficult to form than the five-membered ring system and this transformation ascribed to the poor ability of 1,7-enynes to function as bidentate ligands. A built-in benzene linker may benefit the coordination and satisfy this transformation (Scheme 3) [19]. Tanaka et al. recently reported a Pd(0)-catalyzed tandem cyclization of allenenes [20]. An aryl halide was employed with a Pd(0) species to form an oxidative addition intermediate, which in turn reacts with an allene and formed a π -allyl species. The novel intermediate finally reacted with another olefin nucleophilic moiety to form cyclization product.

Nickel–chromium based catalytic systems can promote cycloisomerization of 1,6- or 1,7-enynes [21]. To achieve enough catalytic activity, the catalyst is attached to an insoluble phosphinylated cross-linked polystyrene. Although the mechanism remains unclear, the reaction seems to proceed similar to the Pd(0)–Pd(II) system and is efficient in the formation of both five- and six-membered rings. A

key feature of this system is the cycloisomerization of enallenes to afford 1,4-dienes exclusively [22]. A catalytic Co(I) system with a trimethyl phosphite as the ligand has been reported for formation of vinyl cyclopentenones and dihydrofurans [23]. Co(I) complexes such as $\text{CpCo}(\text{CO})_2$ can also catalyze another ene type reaction, the Conia reaction, leading to the formation of functionalized methylenecyclopentanes [24]. Although transition metal complexes have long been used extensively for cyclization of enynes, no catalytic or mediated cycloisomerizations were available until Buchwald et al. reported a titanium-based system [25]. Whereas the trans olefins are converted to 1,4-dienes with good yields, the cis olefins are only partially converted to cyclopentenones or do not react. The catalytic cycle was also proposed to involve formation of titanacyclopentene, β -hydride elimination, and reductive elimination steps. They also reported an example of the cycloisomerization of diene-ynes to 1,4,5-trienes.

Murai et al. showed that the cycloisomerization of enynes catalyzed by PtCl_2 has several feasible pathways: (1) to 1,3-dienes via a formal metathesis, (2) to a 1,4-diene if the enyne substrates contains an allylsilane or stannane, (3) to a homo-allylic ether if it the reaction is performed in an alcoholic medium, or (4) to bicycle[4.1.0]heptene derivatives (Scheme 4) [26]. Further studies conducted by other groups have indicated the cyclization might proceed via a cationic mechanism triggered by coordination of Pt(II) with the alkyne moiety [27, 28]. Very recently, Oi and coworkers also observed a formal metathesis reaction mediated by a cationic Pt complex [29].

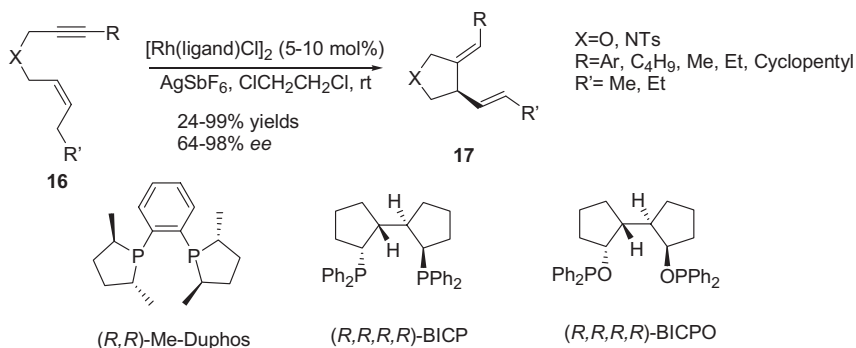


Scheme 4. Platinum-based catalytic system.

A ruthenium based catalytic system was developed by Trost and coworkers and used for the intermolecular Alder–ene reaction of unactivated alkynes and alkenes [30]. In initial attempts to develop an intramolecular version it was found that $\text{CpRu}(\text{COD})\text{Cl}$ catalyzed 1,6-enyne cycloisomerizations only if the olefins were monosubstituted. They recently discovered that if the cationic ruthenium catalyst $\text{CpRu}(\text{CH}_3\text{CN})_3^+\text{PF}_6^-$ is used the reaction can tolerate 1,2-di- or tri-substituted alkenes and enables the cycloisomerization of 1,6- and 1,7-enynes [31]. The formation of metallacyclopentene and a β -hydride elimination mechanism was proposed and the cycloisomerization product was formed in favor of the 1,4-diene. A

C–H activation pathway cannot be ruled out for this transformation, however. They subsequently observed C–H insertion of a *cis* substituent by means of isotope studies [32]. The cycloheptene product was observed as the major product when *cis*- or tri-substituted enyne and acetylenic ester termini were present. Ruthenium hydride catalysts reported by Mori and Dixneuf can also initiate the cycloisomerization of 1,5- and 1,6-enynes and dienes [33, 34]. The vinylruthenium hydride can be obtained from $\text{RuClH}(\text{CO})(\text{PPh}_3)_3$ or in the presence of acetic acid or ethanol.

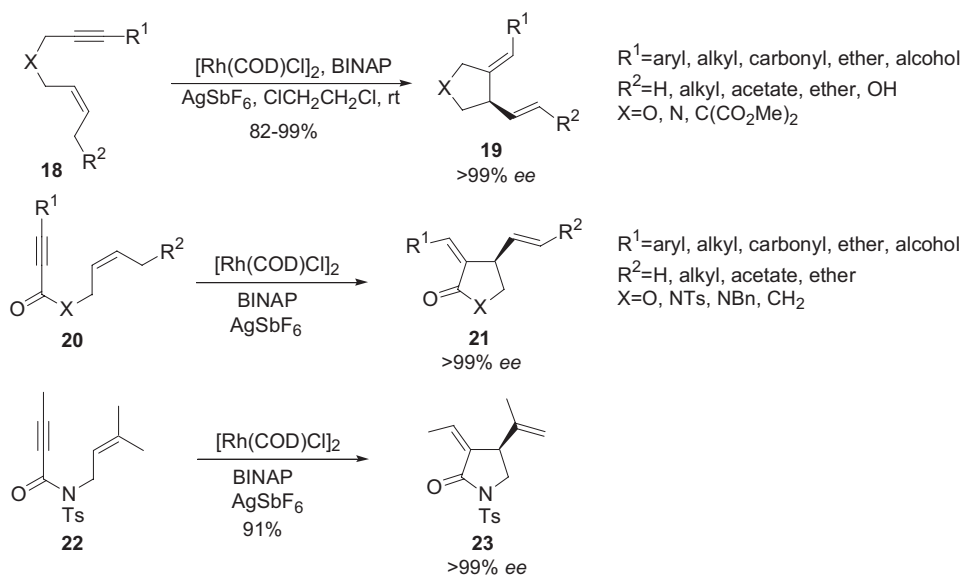
Rh-catalyzed 1,6-enyne cycloisomerization using Wilkinson's catalyst has been reported; an endo-type cyclization product was obtained [35]. As noted by Grigg, insertion of Rh into a terminal alkyne C–H unit is critical for generating an $\text{Rh}(\text{III})\text{-H}$ species for hydorrhodation. A new, highly efficient, and selective rhodium-catalyzed heteroatom-tethered 1,6-enyne cycloisomerization has recently been reported by Zhang et al. [36–41]. The key feature of this reaction is the generation of a highly coordinated unsaturated Rh moiety to facilitate the formation of the metallacyclopentene. The catalyst precursors involved are $[\text{Rh}(\text{dppb})\text{Cl}]_2$, $[\text{Rh}(\text{BICP})\text{Cl}]_2$, $[\text{Rh}(\text{BICPO})\text{Cl}]_2$, and $[\text{Rh}(\text{Me-Duphos})\text{Cl}]_2$. The cationic catalysts were prepared by reaction of the dimer with AgSbF_6 in the presence of an enyne substrate [36]. It is worth noting that only 1,4-dienes **17** are formed and that substrate scope is generally broad compared with other systems. The first enantioselective version of Rh-catalyzed cycloisomerization was also reported by Zhang et al. High enantioselectivity has been observed (64–98 % *ee*). For example, up to 98 % *ee* has been achieved with $[\text{Rh}(\text{BICP})\text{Cl}]_2$ catalyst (Scheme 5) [37]. The catalytic systems are, however, still very responsive to the subtle changes of the electronic nature of the substrates and chiral ligands.



Scheme 5. The first rhodium-catalyzed enantioselective enyne cycloisomerization.

A new catalytic system has been found – simply mixing $[\text{Rh}(\text{COD})\text{Cl}]_2$ and chiral bidentate ligands (BINAP or TunePhos) in situ led to a significant improvement (Scheme 6) [38–41]. The non-coordinate solvent 1,2-dichloroethane and the counter-ion SbF_6^- still play an important role in this system. Surprisingly, no reactivity was observed at room temperature with the $[\text{Rh}(\text{BINAP})\text{Cl}]_2$ precatalyst, whereas the in situ $[\text{Rh}(\text{COD})\text{Cl}]_2/\text{BINAP}$ system is very efficient and achieved

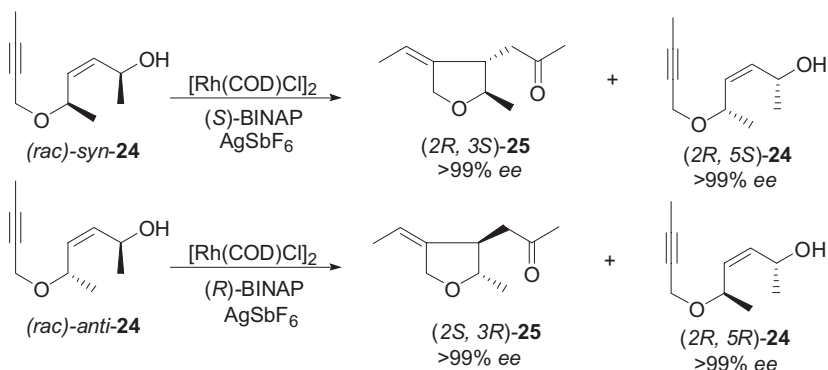
ideal enantioselectivity for several prototypical substrates containing nitrogen, oxygen, and carbon linkages (99 % ee). Moreover, high turnover numbers (up to 1500 h^{-1}) have been observed under very mild conditions [38]. Substrate scope has been broadened by applying this new procedure to the cycloisomerization of a variety of enynes. Highly functionalized γ -lactones, γ -lactams, tetrahydrofurans, pyrrolidines, and carbocyclic systems are formed. These transformations have broad functional group tolerance and enable direct access to vinyl ethers, vinyl acetates, allylic ethers, enamides, methyl ketones, and aldehydes with high enantioselectivity. Trisubstituted enyne amides were also tested and resulted in excellent enantioselectivity and conversion [40]. These features will be very useful for applications in effective organic synthesis. A number of formal natural product syntheses have also been carried out to demonstrate the power of this catalytic system.



Scheme 6. Asymmetric Rh-catalyzed cycloisomerization reaction via a new procedure.

A highly stereoselective kinetic resolution process for Rh-catalyzed enyne cycloisomerization has also been developed by Zhang et al. [41]. This transformation has enabled the highly enantioselective synthesis of polyfunctionalized tetrahydrofurans and lactones with two or three adjacent stereocenters and it is regarded as a major breakthrough in enynes cycloisomerization and in kinetic resolution (Scheme 7).

As variations of Rh-catalyzed cycloisomerization Widenhoefer and coworkers have developed asymmetric 1,6-enyne cyclization/hydrosilylation reactions by using the Rh(I)/biphemp system; excellent de and ee were obtained [42]. Brummond et al. also discovered a rhodium(I)-catalyzed allenic Alder–ene reaction that



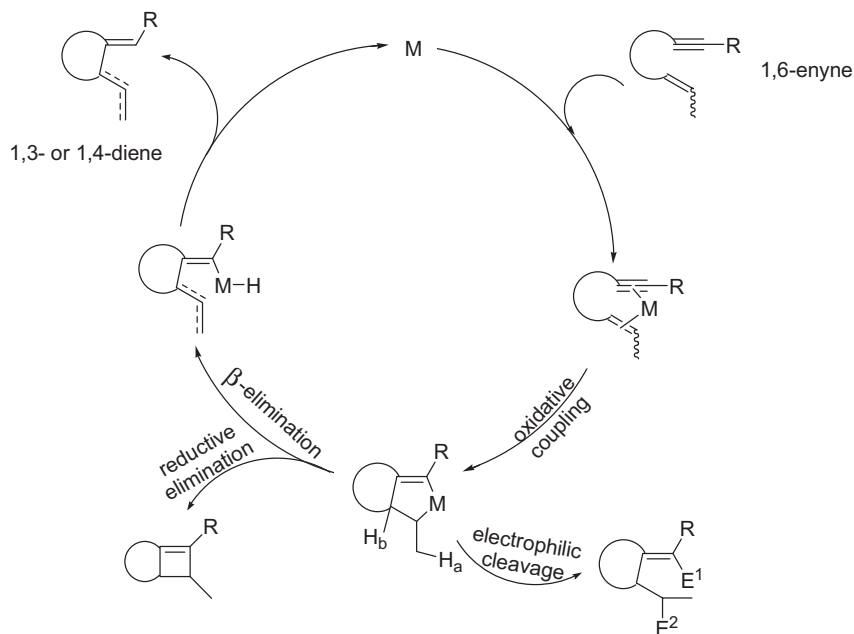
Scheme 7. Rh-catalyzed kinetic resolution of enyne cycloisomerization.

provides cross-conjugated trienes in good yields (45–93 %) [43]. Murai reported the iridium complex $[\text{IrCl}(\text{CO})_3]_n$ -catalyzed cycloisomerization of acetylenic unsubstituted 1,6-enynes which provide 1,3-dienes via formal metathesis [44]. These transformations are the starting points of many exciting discoveries.

1.2.5.2 Mechanism

Considering the mechanistic rationales of the transition metal-catalyzed enyne cycloisomerization, different catalytic pathways have been proposed, depending on the reaction conditions and the choice of metal catalyst [3–5, 45]. Complexation of the transition metal to alkene or alkyne moieties can activate one or both of them. Depending on the manner of formation of the intermediates, three major mechanisms have been proposed. The simultaneous coordination of both unsaturated bonds to the transition metal led to the formation of metallacycles, which is the most common pathway in transition metal-catalyzed cycloisomerization reactions. Hydrometalation of the alkyne led to the corresponding vinylmetal species, which reacts in turn with olefins via carbometalation. The last possible pathway involves the formation of a π -allyl complex which could further react with the alkyne moiety. The π -allyl complex could be formed either with a functional group at the allylic position or via direct C–H activation. Here the three major pathways will be discussed in a generalized form to illustrate the mechanisms (Scheme 8).

Metallacyclopentenes have been formed with a large number of transition metals and unsaturated substrates [46]. The main steps of the proposed catalytic cycle start with coordination of an enyne to the metal center; oxidative coupling then leads to a metallacyclopentene intermediate (Scheme 8) [40]. This intermediate can undergo several transformations: β -hydride elimination, reductive elimination, and electrophilic cleavage by different electrophiles. The β -hydride elimination is the most common process and gives 1,3- or 1,4-dienes depending on the regioselectivity of the elimination step. It is known that β -hydride elimination requires a vacant coordination site on the metal in the cis relationship between the C–M bond and C–H bond. Ideally, these bonds should be aligned to optimize

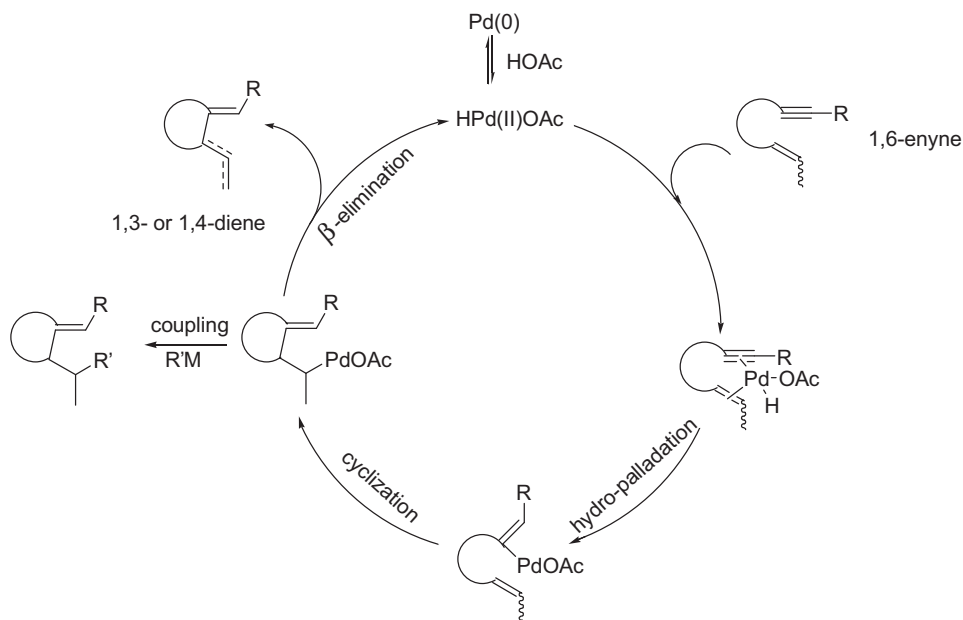


Scheme 8. Metallacyclopentene pathway.

orbital overlap [47, 48]. Stereochemically, alignment of C–H_a bond for insertion is better than a C–H_b bond, although the energy barrier is higher (H_b is in the allylic position). Ru, Pd, Co, Ir, and Rh have been reported to undergo this pathway and the selectivity of 1,3- vs. 1,4- diene is highly dependent on the nature of the transition metal, the form of precatalyst, and the steric and electronic features of the substrates.

Addition of an R–M species to an alkyne triple bond led to the formation of a vinylmetal moiety, which will subsequently react with the alkene. The R group can be hydrogen, tin, boron, and even halogen atoms [49–51]. Ruthenium and palladium are the most common used transition metals for this pathway. In the presence of a carboxylic acid, a Pd(0) species generates a Pd(II) hydride which is the active catalyst during the cycloisomerization (Scheme 9). After coordination of the latter to 1,6- or 1,7-enynes, hydrometalation provides the vinylmetal that is ready to undergo cyclization. The resulting intermediate can go through a β -hydride elimination to afford a 1,3- or 1,4-diene and regenerate the Pd(II) hydride species. Unlike the metallacyclopentene pathway, the oxidation state of the metal remains unchanged during the catalytic cycle. Ruthenium hydride catalysts behaved in a similar fashion to Pd(II) hydride during the cycloisomerization reactions [52].

The last plausible pathway is a π -allylmetal pathway. π -Allylmetal species are well known in organometallic chemistry for alkylations and cyclizations [53]. This pathway is not common for enyne cycloisomerization and most examples available in the literature are associated with the cyclization of polyenes [54, 55]. The



Scheme 9. Vinylmetal pathway.

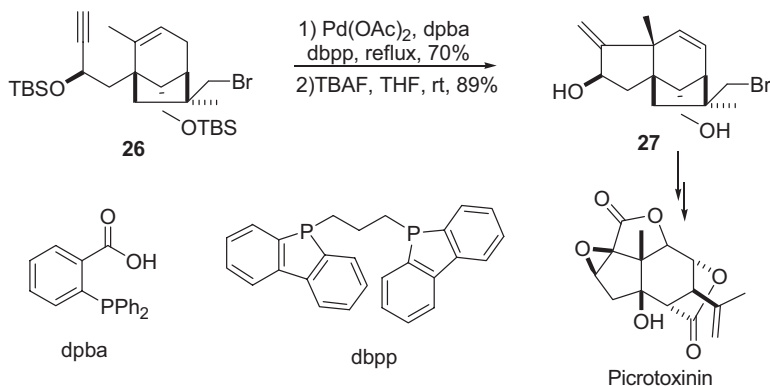
π -allyl complex can be generated after cyclization, as suggested by Takacs in a Fe(0)-catalyzed cyclization of polyenes. It also can be preformed if an active functional group is present in the allylic position. The palladium-catalyzed intramolecular cycloisomerization reaction of allylic acetates is an efficient method for constructing five- or six-membered rings [56, 57]. An asymmetric approach to this transformation has been studied and so far only poor enantioselectivity has been achieved (0–20 % ee) [58]. Very recently, Zhang et al. also reported a Rh-catalyzed cycloisomerization involving a π -allylrhodium intermediate formed from an allylic halide [59].

Compared with cycloisomerization, enyne metathesis as a bond reorganization of an alkene and an alkyne to produce a 1,3-diene is less studied. A recent review by Diver and Giessert highlights some recent advances in synthetic applications, and mechanistic features [60].

1.2.5.3 Applications and Limitations

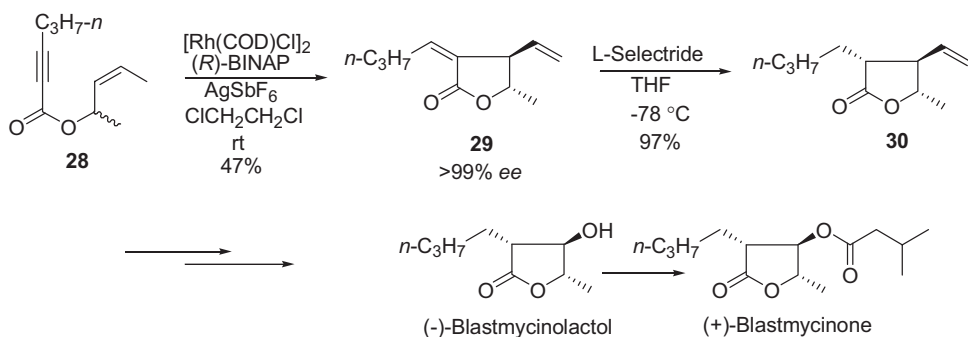
The development of new synthetic methods for efficient synthesis of complex molecules is becoming increasingly important. Transition metal-catalyzed cyclization reactions, especially cycloisomerizations, are very powerful methods for constructing five-, six-, or even seven-membered rings [61]. The advantages of using a transition metal catalyst are not only reduced reaction temperature and broadening the scope of substrates but also the opportunities to increase chemo-, regio-, and enantioselectivity. In the last two decades different transition metals have

been used in catalytic cycloisomerizations and many synthetic methods have been developed in natural product syntheses, demonstrating the synthetic utility of the methods [62–67]. A few syntheses of complex molecules show the potential of transition metal-catalyzed cycloisomerizations.



Scheme 10. Cycloisomerization approach to the picrotoxanes.

The picrotoxane sesquiterpenes are a family of natural products from a poisonous berry *Menispermum cocculus* which were documented as early as the 1600s by Indian natives who used them to stun fish and kill body lice. Trost and coworkers reported an approach to total synthesis of this family based on Pd-catalyzed cycloisomerization [68, 69]. Several synthesis recipes were tested and it was found that a combination of dbpp with a ligand capable of internal proton delivery (dpba) gave the best result and provided a key intermediate **27** for total syntheses of corianin, picrotoxinin, picrotin, and picrotoxate (Scheme 10).



Scheme 11. Formal synthesis of blastmycinolactol and blastmycinone.

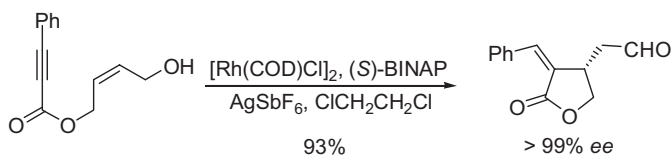
(+)-Blastmycinone is a degradation product of the macrocyclic dilactone (+)-antimycin, an antifungal antibiotic isolated from a family of *Streptomyces* species [70]. The three adjacent chiral centers in a γ -lactone unit pose a significant challenge for synthetic chemists. Recently Zhang et al. successfully employed a novel

Rh-catalyzed cycloisomerization and a kinetic resolution process to conduct a formal synthesis (Scheme 11). Starting from the easily accessed enyne ester **28**, a kinetic resolution process gives a highly functionalized γ -lactone **29** with excellent enantioselectivity. Considering the ideal yield can only be as high as 50 %, this transformation is very efficient. Further reduction of the exo-methylene proved highly selective and the three adjacent chiral center unit **30** could be obtained in high yield [71].

Although incorporation of heteroatoms is often regarded as the Achilles' heel of many metal-catalyzed reactions, transition metal-catalyzed cycloisomerizations, especially with Pd and Rh, are extremely tolerant of varieties of heteroatoms and of functionality. Ru, Ni, and Zr-catalyzed cycloisomerizations also have potential utility in natural product synthesis [72–74]. Transition metal-catalyzed enyne cycloisomerization is one of the most efficient methods for synthesis of a variety of carbocyclic and heterocyclic compounds. The intramolecular version of the catalytic Alder–ene reaction is a very powerful method for construction of mono- or polycyclic ring systems. In the last few decades extensive work by many groups has resulted in great successes. Asymmetric variants are still needed for many transition metals, for example Ru, Ir, however. Enyne cycloisomerizations are still usually highly substrate-dependent. Chiral phosphine ligands and metal precatalysts still need to be studied thoroughly to improve enantio- and regioselectivity. In general, transition metal-catalyzed cycloisomerization is a field full of opportunities and challenges.

Experimental

Rh-catalyzed Asymmetric Cycloisomerization Reaction: Synthesis of (3-Oxo-2-pentylidenecyclopentyl)acetaldehyde



In a dried 25-mL Schlenk tube under nitrogen atmosphere a mixture of $[\text{Rh}(\text{COD})\text{Cl}]_2$ (25 mg, 0.05 mmol) and (*S*)-BINAP (69 mg, 0.11 mmol) were dissolved in 10 mL 1,2-dichloroethane and stirred at room temperature for 1 min. Phenylpropynoic acid 4-hydroxybut-2-enyl ester (194 mg, 1.0 mmol) was then added into the solution at room temperature under nitrogen atmosphere. After stirring for 1 min, a solution of AgSbF_6 (68 mg, 0.2 mmol) in 2 mL 1,2-dichloroethane was added into the mixture in one portion via a syringe. The resulting turbid solution was stirred at room temperature for 5 min, when TLC indicated all starting material was consumed and the reaction was completed. The reaction mixture was directly subjected to column chromatography (silica gel, hexane–ethyl acetate,

85:15) to afford 180 mg (93 % yield, 99 % ee (*S*)) of a colorless oil. ^1H NMR (360 MHz, CDCl_3) δ 9.83 (s, 1H), 5.54 (dt, $J = 2.3, 7.4$ Hz, 1H), 3.22–3.20 (m, 1H), 2.70–2.49 (m, 4H), 2.34–2.16 (m, 3H), 1.57–1.47 (m, 1H), 1.39–1.20 (m, 4H), 0.87 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (90 MHz, CDCl_3) δ 207.61, 138.05, 49.28, 38.74, 36.85, 31.85, 27.83, 27.31, 22.76, 14.27; MS m/z : 195.1 [$\text{M}^+ + 1$]; HRMS (APCI) Calcd. For $\text{C}_{12}\text{H}_{19}\text{O}_2$ [$\text{M}^+ + 1$]: 195.1385, found: 195.1395; The enantiomeric excess was determined by GC on a Gamma 225 column at 170 °C, 1.5 mL min $^{-1}$; $t_1 = 12.92$ min, $t_2 = 13.23$ min, >99 % ee; (*S*)-(+): $[\alpha]_D^{25} = +4.20^\circ$, ($c = 1.0$, CHCl_3).

1.3

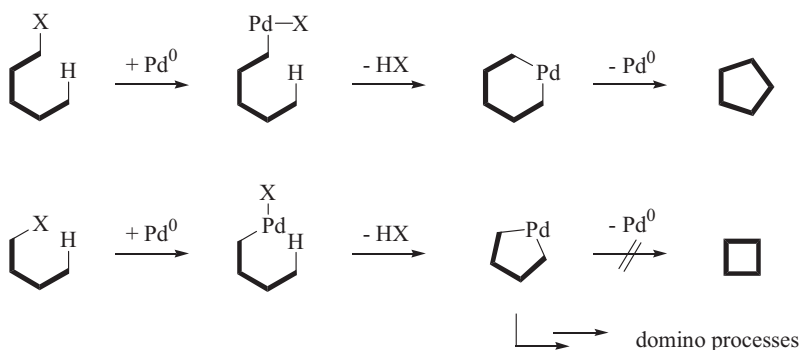
C–H Transformation at Functionalized Alkanes via Palladacycles

Gerald Dyker

1.3.1

Introduction and Fundamental Examples

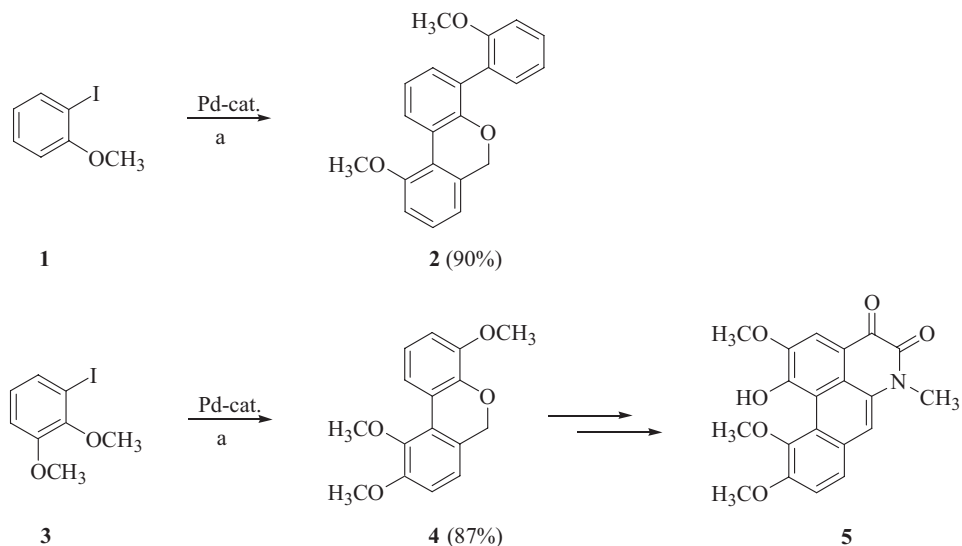
A sequence of oxidative addition and cyclopalladation is a straightforward way for assembling palladacycles [1, 2]. The starting materials for this purpose have to fulfill two structural requirements: (1) a carbon–halogen bond (or alternatively a triflate) at a position where β -hydrogen elimination is prohibited as the subsequent step after oxidative addition (this is of course true for aryl halides) and (2) a carbon–hydrogen bond (either sp^3 - or sp^2 -centered, with the latter discussed in Section III.1.7) has to be in an appropriate distance from the halide. Thus, 6-membered and 5-membered palladacycles are regularly generated as reactive intermediates as outlined in Scheme 1.



Scheme 1. Palladacycles and their ring-size-dependent reactivity (general pictogram).

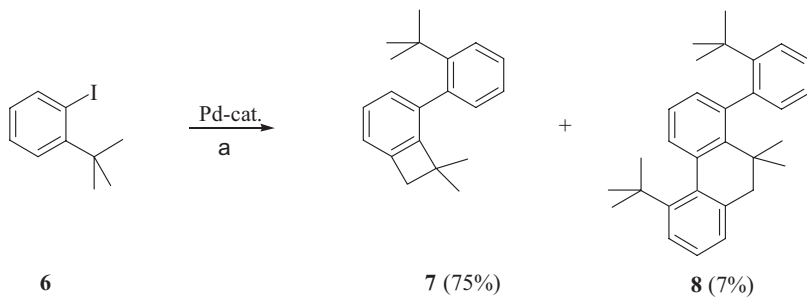
Whereas 6-membered palladacycles readily undergo reductive elimination to give 5-membered rings as final products, the analogous process to give 4-membered carbocycles from 5-membered palladacycles is less feasible, although not completely ruled out, and restricted to special cases (see, for instance, product 7 in

Scheme 3). Instead 5-membered palladacycles can react with a second equivalent of starting material or with additional coupling components resulting in domino processes. Examples of this kind, which involve C–H transformation at sp^2 -centered C–H groups, are presented in Section III.2.4 (cyclometallation at alkenes) and with modifications of the initial steps in Section III.1.7.2 (carbometallation/cyclometallation sequences). The homo-coupling reaction of three equivalents of **1** to give the terphenyl **2**, in excellent yield, was the first example of this kind including C–H activation at an alkyl group, in this case a methoxy group. With an additional substituent in a blocking position, as in substrate **3**, the process stops at the stage of the biphenyl compound. The usefulness of this domino process has already been demonstrated by the successful synthesis of the cytotoxic isoquinoline alkaloid **5** starting from the functionalized biphenyl **4** (Scheme 2) [4].



Scheme 2. C–H transformation at methoxy groups:

(a) 4 mol% Pd(OAc)₂, K₂CO₃, *n*-Bu₄NBr, DMF, 100 °C, 3 days.



Scheme 3. C–H transformation at *t*-butyl groups:

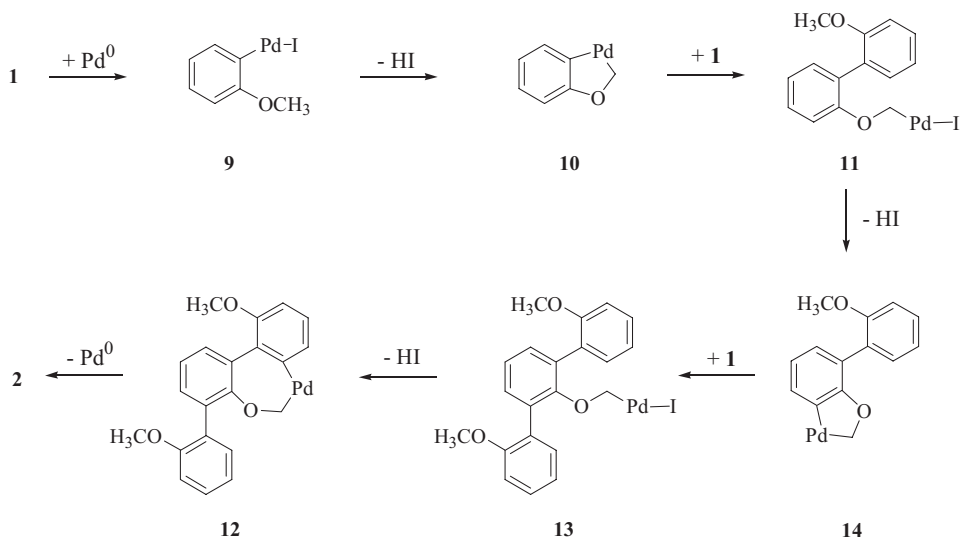
(a) 2.5 mol% Pd(OAc)₂, K₂CO₃, *n*-Bu₄NBr, DMF, 110 °C, 4 days.

This type of C–H transformation is also feasible at the notoriously unreactive *t*-butyl group, as outlined in Scheme 3. After a slight increase of the temperature compared with the reaction conditions for C–H transformation at methoxy groups the process proceeds smoothly. The terphenyl **8** is obviously analogous to compound **2**, whereas the benzocyclobutene **7** as the main product results from reductive elimination of a palladacycle, a step which minimizes steric pressure while obviously building up ring strain.

1.3.2

Mechanism

By analogy with the general pictogram in Scheme 1 the formation of palladacycle **10** from 2-iodoanisole **1** is explained by an oxidative addition/cyclopalladation sequence. Addition of the second equivalent of **1** to the palladacycle **10** either involves Pd(IV) intermediates or a ligand-exchange reaction between the complexes **9** and **10**. A second cyclometallation leads to palladacycle **14**, which of course has the same reactivity as **10**, namely adding the third equivalent of **1** to give the symmetric intermediate **13**. After another cyclometallation step the domino process is completed by reductive elimination, simultaneously setting free the active catalyst. This mechanistic scheme also enables the formation of the biaryl compound **3** to be easily understood; in this reaction an additional methoxy group is blocking the crucial position for formation of the second palladacycle (by analogy with **14**).



Scheme 4. General mechanistic pathway of the domino process to dibenzopyrane **2** (additional ligands omitted).

1.3.3

Scope and Limitations

In addition to methoxy groups benzyloxy groups also have been tested as targets for this type of C–H transformation and, indeed, substrate **15** reacts in the same way as its simpler congener **1**. As an example for an annulated substrate the naphthalene derivative **17** reacts with participation of its peri position to give naphthofuran **18**. The reactivity of *t*-butyl groups has already been demonstrated in Scheme 3. In contrast, thiomethoxy groups are inert under these reaction conditions.

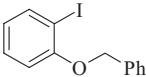
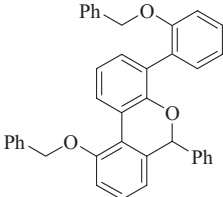
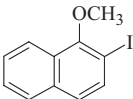
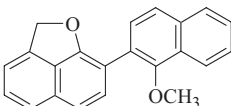
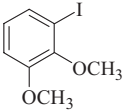

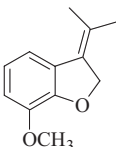
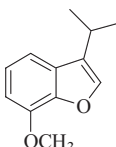
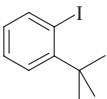

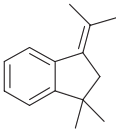
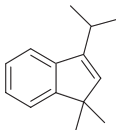
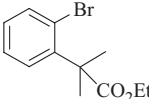
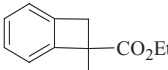
Cross-coupling reactions are also possible as an extension of this type of domino process – with excess vinyl bromide **19** either benzofurans **20** or indenenes **21** are obtained as mixtures of double-bond isomers [5, 6].

Aryl bromides of type **22** have also recently been successfully converted by C–H transformation to give benzocyclobutenes [8].

Experimental**10-Methoxy-4-(2-methoxyphenyl)-6H-dibenzo[*b*]pyran (**2**)**

A mixture of 468 mg (2.00 mmol) 1-iodo-2-methoxybenzene (**1**), 1.1 g (8.0 mmol) K_2CO_3 , 645 mg (2.00 mmol) tetra-*n*-butylammonium bromide, 12 mg (53 μ mol) palladium acetate, and 10 mL dry dimethylformamide (DMF) was heated at 100 °C under nitrogen for 3 days (for reasons of convenience a screw-capped tube was used as the reaction vessel). Water (50 mL) was added at room temperature and the mixture was extracted with diethyl ether (3 \times 50 mL; methyl *tert*-butyl ether gives the same result). The combined extracts were filtered through a small pad (~2 g) of silica and concentrated; TLC (silica, petroleum ether (b.p. 35–70 °C)–diethyl ether 4:1): R_F = 0.38, 0.19 (weak). The fraction with R_F = 0.38 was isolated by flash chromatography to give 190 mg (90 %) terphenyl **2** as a colorless solid of m.p. 135 °C. 1H NMR ($CDCl_3$, 300 MHz): δ = 3.78 (s, 3H, 2'-OCH₃), 3.92 (s, 3H, 10-OCH₃), 4.93 (s, 2H, 6-H), 6.75 (d, J = 7.4 Hz, 1H, 7-H), 6.93 (d, J = 8.3 Hz, 1H, 9-H), 6.98 (d, J = 8.5 Hz, 1H, 3'-H), 7.01 (m, 1H, 5'-H), 7.10 (t, J = 7.7 Hz, 1H, 2-H), 7.20 (dd, J = 7.5, 1.7 Hz, 1H, 3-H), 7.22 (t, J = 7.9 Hz, 1H, 8-H), 7.26 (m, 1H, 6'-H), 7.33 (m, 1H, 4'-H), 8.39 (dd, J = 7.9, 1.7 Hz, 1H, 1-H).

Table 1. Examples of the structural diversity of this type of coupling process.

Starting materials	Products	Yield (%)	Ref.		
 15	 16	64	2		
 17	 18	71	7		
 3	 19 (10 equiv.)	 20a	 20b	82	6
 6	 19 (10 equiv.)	 21a	 21b	63	5
 22	 23	60	8		

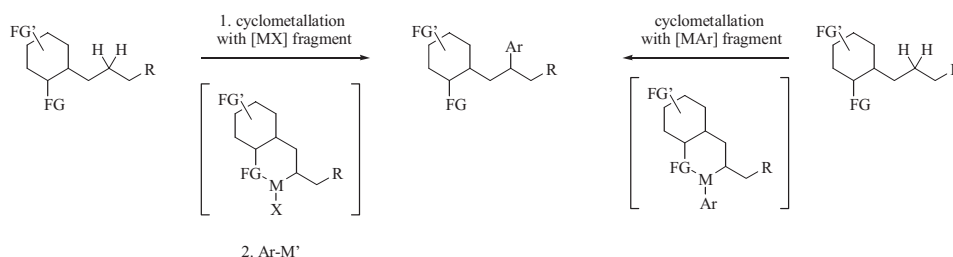
1.4

CH Transformation at Functionalized Alkanes via Cyclometalated Complexes*Bengü Sezen and Dalibor Sames*

1.4.1

Introduction and Fundamental Examples

Because of the creative minds contributing to the field, the tools of C–H bond transformation available to synthetic chemists are actively expanding [1]. Among these, coordination-directed C–H bond-activation has long preserved its appeal, because it enables selective functionalization of a particular C–H bond in the presence of other functional groups. This can be achieved by using a heteroatom (FG = functional group shown in Scheme 1) in the substrate structure to direct the metal complex to the proximity of the specific C–H bond. Even unactivated sp^3 -centered C–H bonds tend to react in a cyclometalation step with palladium, platinum [2], and ruthenium catalysts [3].



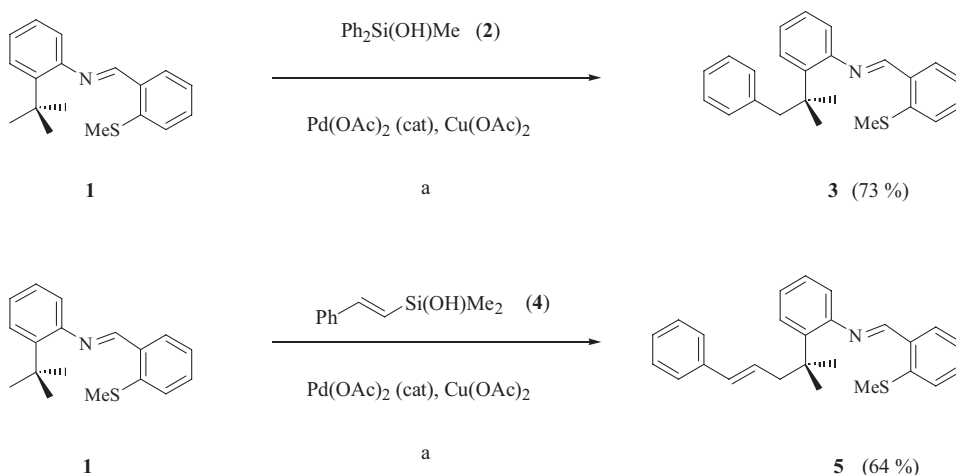
Scheme 1. Metallacycles as intermediates in C–H to C–C transformations.

Accordingly, the C–H bond activation/arylation methodology on which this book is focusing requires a strong chelating group in the substrate structure that can coordinate with the [M–X] or [M–Ar] intermediate and bring it in close proximity of the C–H bond. Moreover, substrates must be designed to form a cyclometalated intermediate that will facilitate the subsequent C–C bond-formation step [4] but at the same time is stable enough to enable the C–H bond activation process. Six membered ring cyclopalladated intermediates have proved to have the correct balance to achieve both [5].

In addition to these requirements related to substrate structure, an aryl donor capable of undergoing transmetalation with Pd(II) intermediates under conditions suitable for C–H bond activation is necessary. Among the Ph–BX₂/Ph–SiX₃/Ph–SnX₃ trio, silanols have the desired reactivity. Although monophenyl silanol, silanediol, and silonate can be used as the aryl group donor, diphenylsilanol proved superior.

As an example, Schiff base 1, with its bidentate chelation separated by a three-carbon fragment (the correct distance for formation of a six-membered metallacycle) from the C–H bond, can undergo palladium-catalyzed C–H bond arylation

with diphenyl silanol **2** (Scheme 2) [6]. Furthermore, this method of arylation can be extended to alkenylation as exemplified by the successful coupling of **1** with styrenyl silanol **4**. The functionalization is exclusively observed in the most unreactive part of the molecule, the *t*-butyl group; leaving the more reactive C–H bonds and functional groups in the substrate structure intact. This demonstrates the high level of selectivity obtained via chelation assistance. Moreover, the C–H transformation reaction stops at the mono-functionalization level, the phenyl or styrenyl group introduced in the process serves to disfavor subsequent activation of the product at the newly formed benzylic or allylic methylene or the second methyl group. The explanation of this observation is not straightforward. Perhaps the introduced phenyl ring or alkene coordinates to the palladium metal leading to formation of a stable and unreactive palladium complex. Alternatively, the additional steric bulk in products **3** and **5** disfavors interaction of the Pd metal even with a very reactive benzylic C–H bond.



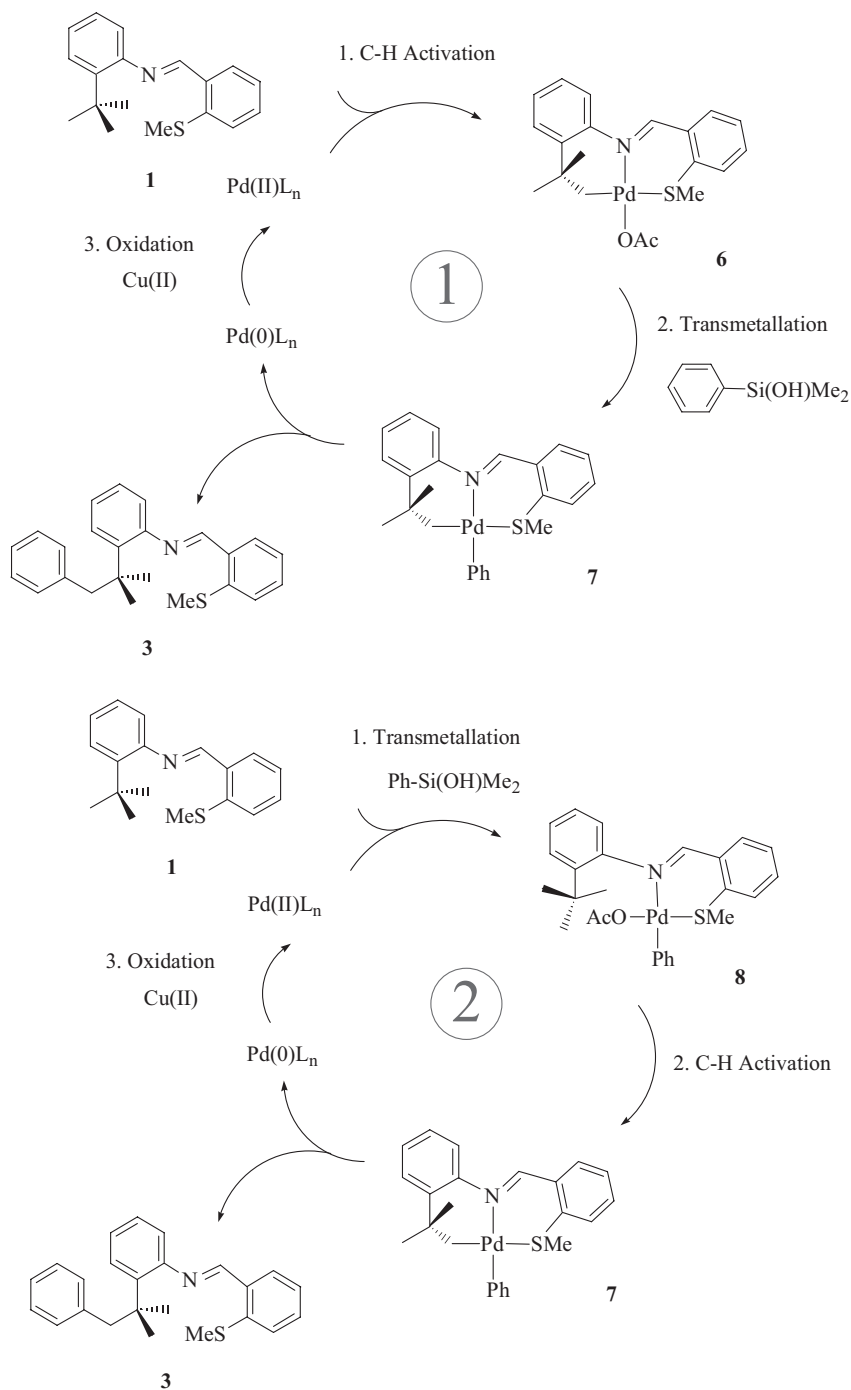
Scheme 2. Arylation and alkenylation of *t*-butyl groups.

Conditions: (a) substrate (0.02 M), silanol (2 equiv.), $\text{Pd}(\text{OAc})_2$ (4 mol%), benzoquinone (4 mol%), $\text{Cu}(\text{OAc})_2$ (2 equiv.), DMF, 100 °C.

1.4.2

Mechanism

Two closely related yet distinct pathways can be proposed for the arylation of C–H bonds based on coordination-directed C–H bond activation: (1) cyclometalation with an MX_n fragment followed by transmetalation with $\text{Ar-M}'$ and reductive elimination, or (2) cyclometalation with an ArMX_{n-1} fragment followed by reductive elimination (Scheme 1). Analogously, two catalytic cycles can be written for the current transformation. The first one would be Cycle 1 which proceeds via cyclopalladation (with $\text{Pd}(\text{OAc})_2$) followed by transmetalation (Scheme 3). An alterna-



Scheme 3. Two rational mechanistic pathways for the arylation of *t*-butyl groups.

tive would be catalytic Cycle 2 in which transmetalation precedes the C–H bond-activation step; the metal complex that activates the C–H bond in this scenario would be a Ph–Pd(II) species. Because the cyclopalladated complex **6** was prepared and shown to be inactive in this arylation reaction, we believe that catalytic Cycle 2 is the operative cycle in this process. Thus, Pd(OAc)₂ undergoes transmetalation with Ph₂Si(OH)Me to form a Ph–Pd–OAc intermediate which then coordinates to the substrate and activates the targeted C–H bond. Reductive elimination of the product from the phenyl-substituted complex **7** followed by oxidation of the Pd(0) back to Pd(II) complete the cycle.

Although introduced separately, transmetalation (catalytic Cycle 2) and cyclopalladation (catalytic Cycle 1) were found to be competitive processes under given arylation reaction conditions. Because **6** is ineffective in catalyzing the desired transformation, any condition that favors its formation (fast C–H bond activation before transmetalation) would inhibit the arylation process. Thus, substrates that form stable five membered cyclopalladated complexes will fail to undergo the arylation reaction (see Section 1.4.3).

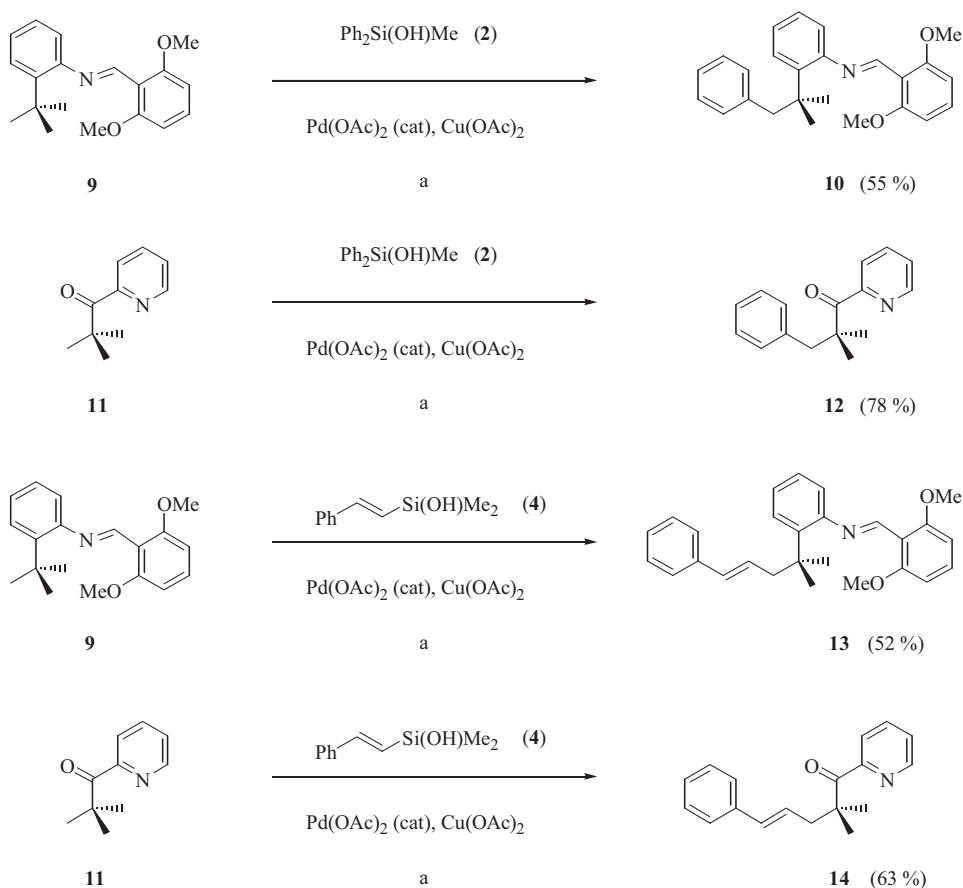
Moreover, the rate of transmetalation must be in accord with this scenario. Silanols work best because they undergo transmetalation fast enough to avoid prior cyclopalladation (faster than boronic acids which fail to induce catalytic Cycle 2, affording **6**), however at the same time not fast enough to favor a second transmetalation and biaryl formation over desired pathway to the phenyl-substituted complex (cf. **7**, catalytic cycle 1; phenyl stannanes, for example, form biphenyl as major product.).

1.4.3

Scope and Limitations

In addition to Schiff base **1**, a similar structure, Schiff base **9** reacts under catalytic arylation conditions to give product **10** in 55 % yield (Scheme 4). Presumably reduced stability of the palladium chelate on exchange of the thiomethoxy group for methoxy is responsible for the reduced yield. Pyridine is another structure that can function as a directing group in this arylation reaction, showing the feasibility of monodentate substrates to undergo this transformation. Product **12** was obtained in 78 % yield from pivaloyl pyridine **11**. Furthermore, the same substrates **9** and **11** can be coupled with styrenyl silanol **4** via this Pd catalyzed C–H bond activation process.

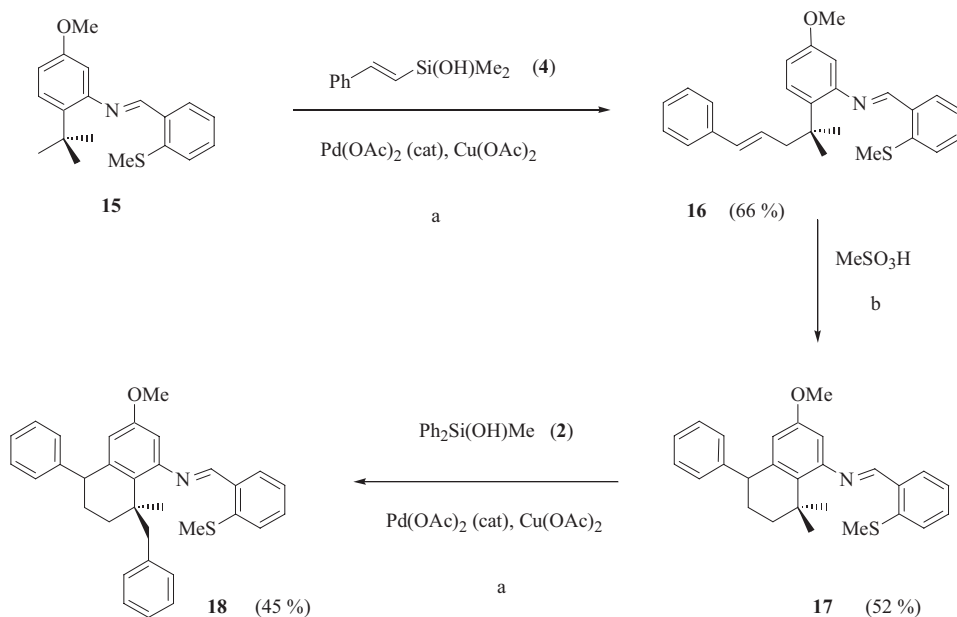
The scope of this method can best be exemplified by the following tandem alkenylation–arylation sequence. Schiff base **15** undergoes a mono-coupling reaction with styrenyl silanol **4** to give **16** selectively in 66 % yield; **16** can then cyclize under acidic conditions to form **17**. Although **16** is inert under these catalytic C–H transformation conditions, **17** can be mono-arylated at the second methyl group to give product **18**.



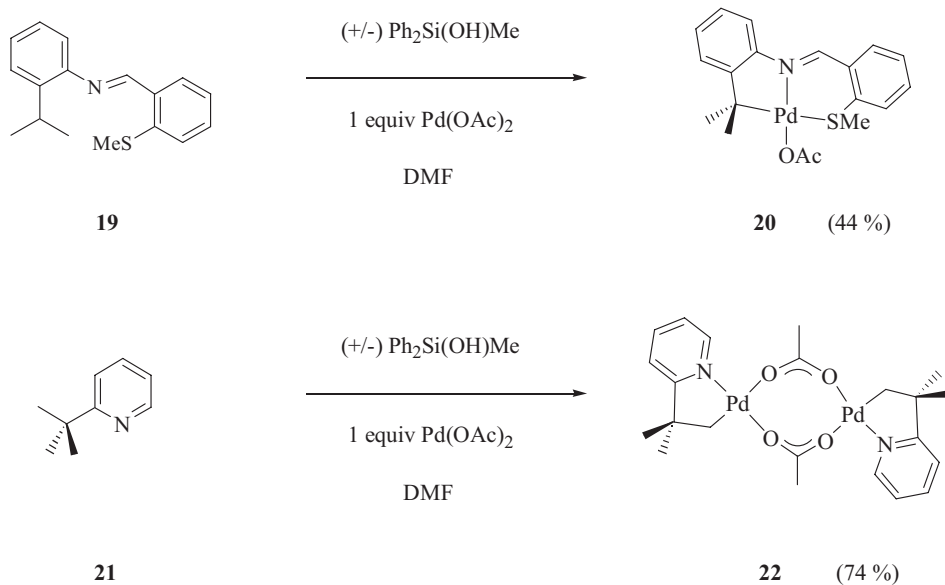
Scheme 4. Scope of arylation and alkenylation procedure.

Conditions: (a) substrate (0.02 M), silanol (2 equiv.), $\text{Pd}(\text{OAc})_2$ (4 mol%), benzoquinone (4 mol%), $\text{Cu}(\text{OAc})_2$ (2 equiv.), DMF, 100 °C.

Apart from these successful transformations, the method has its limitations. As already mentioned, the success of this arylation and alkenylation reaction depends on a delicate balance of rates of transmetalation and C–H bond activation. For substrate **19**, rapid benzylic C–H bond activation is favored over formation of the six-membered cyclopalladated intermediate, which in turn gives rise to complex **20** instead of the arylation reaction (Scheme 6). Furthermore, substrate **21**, does not undergo the arylation reaction but follows the competitive pathway to form five membered cyclopalladated complex **22**.



Scheme 5. Tandem alkenylation–arylation sequence.
 Conditions: (a) substrate (0.02 M), silanol (2 equiv.), Pd(OAc)_2 (4 mol%), benzoquinone (4 mol%), Cu(OAc)_2 (2 equiv.), DMF, 100 °C. (b) MeSO_3H , CH_2Cl_2 , RT.



Scheme 6. Limitations of the arylation procedure.

Experimental

DMF was first purified by use of an alumina/copper catalyst solvent purification column and then distilled over P_2O_5 . The glassware used throughout the purification and experimental manipulations was flame dried thoroughly. The reactions were performed under an argon atmosphere in closed systems. (2-*tert*-Butylphenyl)-(2-thiomethylbenzylidene)amine **1** was prepared from 2-*tert*-butylaniline and 2-thiomethylbenzaldehyde in toluene under reflux with continuous azeotropic removal of water. The purity of the Schiff base starting material is important, because trace amounts of remaining free aniline complex with $Pd(OAc)_2$ and reduces yields. Thus, if necessary, the Schiff base can be purified by flash column chromatography (5 % NEt_3 /15 % ethyl acetate/80 % hexanes). The order of addition of the reagents is important to the success of the method and the order mentioned in the procedure must be followed.

Catalytic Arylation of (2-*tert*-Butylphenyl)-(2-thiomethylbenzylidene)amine **1**

In a flame-dried 25-mL round-bottomed flask, $Pd(OAc)_2$ (2.7 mg, 0.012 mmol, 4 mol%) and $Cu(OAc)_2$ (109 mg, 0.6 mmol, 2 equiv.) were dissolved in 5 mL dry DMF and purged with argon. ($Pd(OAc)_2$ and $Cu(OAc)_2$ must be dissolved completely before the following steps.) Diphenylmethyl silanol (129 mg, 0.6 mmol, 2 equiv.) was dissolved in 5 mL dry DMF and added dropwise to this solution. (2-*tert*-Butylphenyl)-(2-thiomethylbenzylidene)amine **1** (85 mg, 0.3 mmol) and benzoquinone (1.3 mg, 0.012 mmol, 4 mol%) dissolved in 5 mL dry DMF were added next and the reaction mixture was heated to 100 °C. The course of the reaction was monitored by TLC and on completion (after approx. 10 h) the crude mixture was treated with Na_2S and filtered through a pad of Celite. DMF was evaporated and the residue was purified by flash column chromatography (5 % NEt_3 /15 % ethyl acetate/80 % hexanes) to give 79 mg product **3** (73 % yield). 1H NMR ($CDCl_3$, 400 MHz): δ = 1.40 (6H, s), 2.53 (3H, s), 3.35 (2H, s), 6.87–6.94 (3H, m), 7.08–7.12 (5H, m), 7.24–7.34 (2H, m), 7.38–7.45 (2H, m), 8.17 (1H, dd, J_1 = 1.3, J_2 = 7.8 Hz), 8.91 (1H, s). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 17.5, 29.2, 40.2, 46.1, 120.1, 125.8, 125.8, 126.1, 126.1, 127.5, 127.9, 128.1, 129.1, 130.9, 132.8, 134.4, 138.9, 140.6, 142.3, 151.9, 156.4.

References to Chapter 1 – C–H Transformation at Functionalized Alkanes

References to Section 1.1.1

- 1 S.-I. Murahashi, T. Naota, *Bull. Chem. Soc. Jpn.* **1996**, 69, 1805–1824.
- 2 S.-I. Murahashi, H. Takaya, *Acc. Chem. Res.* **2000**, 33, 225–233.
- 3 S. Murahashi, *J. Am. Chem. Soc.* **1955**, 77, 6403.
- 4 S.-I. Murahashi, *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 2443–2465.
- 5 T. Naota, H. Takaya, S.-I. Murahashi, *Chem. Rev.* **1998**, 98, 2599–2660.
- 6 S.-I. Murahashi, T. Hirano, T. Yano, *J. Am. Chem. Soc.* **1978**, 100, 348–349.
- 7 S.-I. Murahashi, T. Watanabe, *J. Am. Chem. Soc.* **1979**, 101, 7429–7430.
- 8a T. Naota, H. Taki, M. Mizuno, S.-I. Murahashi, *J. Am. Chem. Soc.* **1989**, 111, 5954–5955.
- 8b S.-I. Murahashi, T. Naota, H. Taki, M. Mizuno, H. Takaya, S. Komiya, Y. Mizuho, N. Oyasato, M. Hiraoka, M. Hirano, A. Fukuoka, *J. Am. Chem. Soc.* **1995**, 117, 12436–12451.
- 9 S. Komiya, Y. Mizuho, N. Kasuga, *Chem. Lett.* **1991**, 2127.
- 10 S. Paganelli, A. Schionato, C. Botteghi, *Tetrahedron Lett.* **1991**, 2807–2810.
- 11 S.-I. Murahashi, K. Take, T. Naota, H. Takaya, *Synlett* **2000**, 1016–1018.
- 12 Y. Lin, X. Zhu, M. Xiang, *J. Organomet. Chem.* **1993**, 215–218.
- 13 M. Hirano, M. Hirai, Y. Ito, T. Tsurumaki, A. Baba, A. Fukuoka, S. Komiya, *J. Organometal. Chem.* **1998**, 569, 3–5.
- 14 K. Mori, T. Hara, T. Mizugaki, K. Ebitani, K. Kaneda, *J. Am. Chem. Soc.* **2003**, 125, 11460–11461.
- 15 M. Sawamura, H. Hamashima, Y. Ito, *J. Am. Chem. Soc.* **1992**, 114, 8295–8296.
- 16 Y. Yamamoto, Y. Kubota, Y. Honda, H. Fukui, N. Asao, *J. Am. Chem. Soc.* **1994**, 116, 3161–3162.
- 17 T. Naota, A. Tanna, S.-I. Murahashi, *J. Am. Chem. Soc.* **2000**, 122, 2960–2961.
- 18 T. Naota, A. Tanna, S. Kamuro, S.-I. Murahashi, *J. Am. Chem. Soc.* **2002**, 124, 6842–6843.
- 19 T. Naota, A. Tanna, S.-I. Murahashi, *Chem. Commun.* **2001**, 63–64.
- 20 H. Takaya, T. Naota, S.-I. Murahashi, *J. Am. Chem. Soc.* **1998**, 120, 4244–4245.
- 21 S.-I. Murahashi, T. Naota, H. Takaya, X. Zhou, to be published.
- 22 H. Takaya, S. Kojima, S.-I. Murahashi, *Org. Lett.*, **2001**, 3, 431.
- 23 S.-I. Murahashi, T. Naota, E. Saito, *J. Am. Chem. Soc.* **1986**, 108, 7846–7847.
- 24 S.-I. Murahashi, S. Sasao, E. Saito, T. Naota, *J. Org. Chem.* **1992**, 57, 2521–2523.
- 25 T. Naota, Y. Shichijo, S.-I. Murahashi, *J. Chem. Soc. Chem. Commun.* **1994**, 1359–1360.
- 26 H. Takaya, K. Yoshida, K. Isozaki, H. Terai, S.-I. Murahashi, *Angew. Chem. Int. Ed.* **2003**, 42, 3302–3304.
- 27 H. Takaya, S.-I. Murahashi, *Synlett* **2001**, 991–994.

References and Notes to Section 1.1.2

- 1 M. B. Smith, J. March, *March's Advanced Organic chemistry, 5th Edition*, pages 1022–1024, Wiley Interscience: New York, **2001**.
- 2 T. Naota, H. Taki, M. Mizuno, S.-I. Murahashi, *J. Am. Chem. Soc.* **1989**, 111, 5954–5955.
- 3 For 1,3 dienes: (a) K. Takahashi, A. Miyake, G. Hata, *Chem. Ind. (London)*, **1971**, 488; (b) K. Takahashi, A. Miyake, G. Hata, *Bull. Chem. Soc. Jpn.* **1972**, 45, 1183–1191; (c) P. W. Jolly, N. Kokel, *Synthesis* **1990**, 771–773. See also: (d) R. Baker, R. J. Popplestone, *Tetrahedron Lett.* **1978**, 19, 3375–3578; (e) B. M. Trost, L. Zhi, *Tetrahedron Lett.* **1992**, 33, 1831–1834; (f) B. M. Trost, V. J. Gerusz, *J. Am. Chem. Soc.* **1995**, 117, 5156–5157.
- 4 D. R. Coulson, *J. Org. Chem.* **1973**, 38, 1483–1490.
- 5 Y. Yamamoto, U. Radhakrishnan, *Chem. Soc. Rev.* **1999**, 28, 199–207.
- 6 For allenes: (a) Y. Yamamoto, M. Al-Masum, N. Asao, *J. Am. Chem. Soc.* **1994**, 116, 6019–6020; (b) Y. Yamamoto, M. Al-Masum, N. Fujiwara, N. Asao, *Tetrahedron Lett.* **1995**, 36, 2811–2814;

- (c) N. T. Patil, N. K. Pahadi, Y. Yamamoto, *Synthesis*, **2004**, 2186–2190; (d) Y. Yamamoto, M. Al-Masum, A. Takeda, *Chem. Commun.* **1996**, 831–832; (e) Y. Yamamoto, M. Al-Masum, *Synlett* **1995**, 969–970; (f) Y. Yamamoto, M. Al-Masum, N. Fujiwara, *Chem. Commun.* **1996**, 381–382; (g) M. Meguro, S. Kamijo, Y. Yamamoto, *Tetrahedron Lett.* **1996**, 37, 7453–7456; (h) S. Kamijo, Y. Yamamoto, *Tetrahedron Lett.* **1999**, 40, 1747–1750. See also: (i) B. M. Trost, V. J. Gerusz, *J. Am. Chem. Soc.* **1995**, 117, 5156–5157.
- 7 For enynes: (a) M. M. Salter, V. Gevorgyan, S. Saito, Y. Yamamoto, *Chem. Commun.* **1996**, 17–18; (b) V. Gevorgyan, C. Kadowaki, M. M. Salter, I. Kadota, S. Saito, Y. Yamamoto, *Tetrahedron* **1997**, 53, 9097–9106.
- 8 For alkynes: (a) I. Kadota, A. Shibuya, Y. S. Gyoung, Y. Yamamoto, *J. Am. Chem. Soc.* **1998**, 120, 10262–10263; (b) N. T. Patil, I. Kadota, A. Shibuya, Y. S. Gyoung, Y. Yamamoto, *Adv. Synth. Catal.* **2004**, 346, 800–804; (c) N. Tsukada, Y. Yamamoto, *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 2477–2480.
- 9 For methylenecyclopropanes: (a) N. Tsukada, A. Shibuya, I. Nakamura, Y. Yamamoto, *J. Am. Chem. Soc.* **1997**, 119, 8123–8124; (b) N. Tsukada, A. Shibuya, I. Nakamura, H. Kitahara, Y. Yamamoto, *Tetrahedron* **1999**, 55, 8833–8844; (c) I. Nakamura, Y. Yamamoto, *Adv. Synth. Catal.* **2002**, 344, 111–129.
- 10 For cyclopropene: I. Nakamura, G. B. Bajracharya, Y. Yamamoto, *J. Org. Chem.* **2003**, 68, 2297–2299.
- 11 For methyleneaziridines: B. H. Oh, I. Nakamura, Y. Yamamoto, *Tetrahedron Lett.* **2002**, 43, 9625–9628.
- 12 Y. Yamamoto, *Heteroatom-Stabilized Allylic Anions*, in: *Comprehensive Organic Synthesis*, Vol. 2, B. M. Trost, I. Fleming (Eds.), pages 55–79, Pergamon Press: Oxford, **1991**.
- 13 J. Tsuji, *Palladium Reagents and Catalysis; Innovations in Organic Synthesis*, pages 297–319, John Wiley, Chichester, **1995**.
- 14 I. Nakamura, N. Tsukada, M. Al-Masum, Y. Yamamoto, *Chem. Commun.* **1997**, 1583–1584.
- 15 (a) R. C. Larock, W. W. Leong, *Addition of H–X Reagents to Alkenes and Alkynes*, in: *Comprehensive Organic Synthesis*, Vol. 4, B. M. Trost, I. Fleming (Eds.), pages 269–327, Pergamon Press: Oxford **1991**; (b) *Catalytic Heterofunctionalization*, A. Togni, H. Grützmacher (Eds.), Wiley-VCH: Weinheim, **2001**; (c) F. Alonso, I. P. Beletskaya, M. Yus, *Chem. Rev.* **2004**, 104, 3079–3160, and references therein.
- 16 (a) D. Savoia, *Amination Reactions Assisted or Catalyzed by Transition Metals*, in: *Houben–Weyl*, Vol. E21e, G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann (Eds.), pages 5356–5394, Georg Thieme Verlag: Stuttgart, **1995**; (b) T. E. Müller, M. Beller, *Chem. Rev.* **1998**, 98, 675–703, and references therein; (c) R. Taube, *Reaction with Nitrogen Compounds: Hydroamination* in: *Applied Homogeneous Catalysis with Organometallic Compounds*, Vol. 1: *Applications*, B. Cornils, W. A. Herrmann (Eds.), pages 513–524, Wiley-VCH: Weinheim, **2002**; (d) H. Schaffrath, W. Keim, *J. Mol. Catal. A: Chemical* **2001**, 168, 9–14; (e) M. Nobis, B. Driefen–Hölscher, *Angew. Chem. Int. Ed.* **2001**, 40, 3983–3985; (f) T. Minami, H. Okamoto, S. Ikeda, R. Tanaka, F. Ozawa, M. Yoshifuji, *Angew. Chem. Int. Ed.* **2001**, 40, 4501–4503; (g) B. F. Straub, R. G. Bergman, *Angew. Chem. Int. Ed.* **2001**, 40, 4632–4635; (h) M. Utsunomiya, R. Kuwano, M. Kawatsura, J. F. Hartwig, *J. Am. Chem. Soc.* **2003**, 125, 5608–5609.
- 17 K. Takahashi, A. Miyake, G. Hata, *Bull. Chem. Soc. Jpn.* **1972**, 45, 1183–1191.
- 18 R. W. Armbruster, M. M. Morgan, J. L. Schmidt, C. M. Lau, R. M. Riley, D. L. Zabrowski, H. A. Dieck, *Organometallics* **1986**, 5, 234–237.
- 19 L. Besson, J. Goré, B. Cazes, *Tetrahedron Lett.* **1995**, 36, 3857–3860.
- 20 (a) M. Al-Masum, M. Meguro, Y. Yamamoto, *Tetrahedron Lett.* **1997**, 38, 6071–6074; (b) M. Meguro, Y. Yamamoto, *Tetrahedron Lett.* **1998**, 39, 5421–5424.

- 21 U. Radhakrishnan, M. Al-Masum, Y. Yamamoto, *Tetrahedron Lett.* **1998**, 39, 1037–1040.
- 22 I. Nakamura, H. Itagaki, Y. Yamamoto, *J. Org. Chem.* **1998**, 63, 6458–6459.
- 23 (a) I. Kadota, A. Shibuya, L. M. Lutete, Y. Yamamoto, *J. Org. Chem.* **1999**, 64, 4570–4571; (b) L. M. Lutete, I. Kadota, A. Shibuya, Y. Yamamoto, *Heterocycles* **2002**, 58, 347–357; (c) L. M. Lutete, I. Kadota, Y. Yamamoto, *J. Am. Chem. Soc.* **2004**, 126, 1622–1623, and references therein.
- 24 (a) E. J. Smutny, *J. Am. Chem. Soc.* **1967**, 89, 6793–6794; (b) H. Yagi, E. Tanaka, H. Ishiwatari, M. Hidai, Y. Uchida, *Synthesis* **1977**, 334.
- 25 Y. Inoue, Y. Ohtsuka, H. Hashimoto, *Bull. Chem. Soc. Jpn.* **1984**, 57, 3345–3346.
- 26 I. Kadota, L. M. Lutete, A. Shibuya, Y. Yamamoto, *Tetrahedron Lett.* **2001**, 42, 6207–6210.
- 27 (a) D. H. Camacho, I. Nakamura, S. Saito, Y. Yamamoto, *Angew. Chem. Int. Ed.* **1999**, 38, 3365–3367; (b) D. H. Camacho, I. Nakamura, S. Saito, Y. Yamamoto, *J. Org. Chem.* **2001**, 66, 270–275.
- 28 (a) E. W. Walker, R. M. Manyik, K. E. Atkins, M. L. Farmer, *Tetrahedron Lett.* **1970**, 11, 3817–3820; (b) D. Rose, H. Lepper, *J. Organomet. Chem.* **1973**, 49, 473–476.
- 29 K. Philippot, D. Devanne, P. H. Dixneuf, *J. Chem. Soc., Chem. Commun.* **1990**, 1199–1200.
- 30 (a) T. Mitsudo, Y. Hori, Y. Yamakawa, Y. Watanabe, *J. Org. Chem.* **1987**, 52, 2230–2239; (b) H. Doucet, B. Martin-Vaca, C. Bruneau, P. H. Dixneuf, *J. Org. Chem.* **1995**, 60, 7247–7255; (c) C. Bruneau, P. H. Dixneuf, *Chem. Commun.* **1997**, 507–512.
- 31 M. Al-Masum, Y. Yamamoto, *J. Am. Chem. Soc.* **1998**, 120, 3809–3810.
- 32 B. M. Trost, W. Brieden, K. H. Baringhaus, *Angew. Chem. Int. Ed. Engl.* **1992**, 31, 1335–1336.
- 33 B. H. Oh, I. Nakamura, Y. Yamamoto, *J. Org. Chem.* **2004**, 69, 2856–2858.

References and Notes to Section 1.1.3.1

- 1 (a) C. J. Cowden, I. Paterson, *Org. React.* **1997**, 51, 1–200; (b) I. Paterson, C. J. Cowden, D. J. Wallace in *Modern Carbonyl Chemistry*, J. Otera, Ed.; Wiley-VCH, Weinheim, **2000**, pp 249–297.
- 2 (a) S. G. Nelson, *Tetrahedron: Asymmetry*, **1998**, 357–389; (b) R. Mahrwald, *Chem. Rev.* **1999**, 99, 1095–1120; (c) E. M. Carreira in *Comprehensive Asymmetric Catalysis*, Vol. 3, E. N. Jacobsen, A. Pfaltz, H. Yamamoto, Eds.; Springer, Heidelberg, **1999**, pp 997–1065; (d) S. E. Denmark, R. A. Stavenger, *Acc. Chem. Res.* **2000**, 33, 432–440.
- 3 C. Palomo, M. Oiarbide, J. M. García, *Chem. Soc. Rev.* **2004**, 33, 65–75.
- 4 D. Machajewski, C.-H. Wong, *Angew. Chem., Int. Ed.*, **2000**, 39, 1352–1374.
- 5 (a) S. Takayama, G. J. McGarvey, C.-H. Wong, *Chem. Soc. Rev.* **1997**, 26, 407–415; (b) J. Liu, C.-H. Wong, *Angew. Chem., Int. Ed.* **2002**, 41, 1404–1407.
- 6 (a) G. Zhong, R. A. Lerner, C. F. Barbas III, *Angew. Chem., Int. Ed.* **1999**, 38, 3738–3741; (b) V. Maggiotti, M. Resmini, V. Gouverneur, *Angew. Chem., Int. Ed.* **2002**, 41, 1012–1014.
- 7 B. Alcaide, P. Almendros, *Eur. J. Org. Chem.* **2002**, 1595–1601.
- 8 (a) Y. M. A. Yamada, N. Yoshikawa, H. Sasai, M. Shibasaki, *Angew. Chem., Int. Ed.* **1997**, 36, 1871–1873; (b) N. Yoshikawa, Y. M. A. Yamada, J. Das, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1999**, 121, 4168–4178.
- 9 (a) N. Yoshikawa, N. Kumagai, S. Matsunaga, G. Moll, T. Ohshima, T. Suzuki, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, 123, 2466–2467; (b) N. Kumagai, S. Matsunaga, N. Yoshikawa, M. Shibasaki, *Org. Lett.* **2001**, 3, 1539–1542; (c) Kumagai, S. Matsunaga, T. Kinoshita, S. Harada, S. Okada, S. Sakamoto, K. Yamaguzhi, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, 125, 2169–2178.
- 10 (a) B. M. Trost, H. Ito, *J. Am. Chem. Soc.* **2000**, 122, 12003–12004; (b) B. M. Trost, E. R. Silcoff, H. Ito, *Org. Lett.* **2001**, 3, 2497–2500; (c) B. M. Trost, H. Ito,

- E. R. Shilcoff, *J. Am. Chem. Soc.* **2001**, 123, 3367–3368; (d) B. M. Trost, V. S. C. Yeh, *Org. Lett.* **2002**, 4, 3513–3516; (e) B. M. Trost, A. Fettes, B. T. Shireman, *J. Am. Chem. Soc.* **2004**, 126, 2660–2661.
- 11 (a) R. Mahrwald, B. Ziemer, *Tetrahedron Lett.* **2002**, 43, 4459–4461.
- 12 T. Suzuki, N. Yamagiwa, Y. Matsuo, S. Sakamoto, K. Yamaguchi, M. Shibasaki, R. Noyori, *Tetrahedron Lett.* **2001**, 42, 4669–4671.
- 13 (a) D. A. Evans, C. W. Downey, J. L. Hubbs, *J. Am. Chem. Soc.* **2003**, 125, 8706–8707. See also: (b) D. A. Evans, J. S. Tedrow, J. T. Shaw, C. W. Downey, *J. Am. Chem. Soc.* **2002**, 124, 392–393.
- 14 (a) C. Juhl, N. Gathergood, K. A. Jørgensen, *Chem. Commun.* **2000**, 221–2212; (b) N. Gathergood, K. Juhl, T. B. Poulsen, K. Thordrup, K. A. Jørgensen, *Org. Biomol. Chem.* **2004**, 2, 1077–1085.
- 15 W. Yao, J. Wang, *Org. Lett.* **2003**, 5, 1527–1530.
- 16 (a) B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, 122, 2395–2396; (b) W. Notz, B. List, *J. Am. Chem. Soc.* **2000**, 122, 7386–7387; (c) K. Sakthivel, W. Notz, T. Bui, C. F. Barbas III, *J. Am. Chem. Soc.* **2001**, 123, 5260–5267; (d) B. List, P. Pojarliev, C. Castello, *Org. Lett.* **2001**, 3, 573–575.
- 17 (a) Z. Tang, F. Jiang, L.-T. Yu, X. Cui, L.-Z. Gong, A.-Q. Mi, Y.-Z. Jiang, Y.-D. Wu, *J. Am. Chem. Soc.* **2003**, 125, 5262–5263; (b) Z. Tang, F. Jiang, X. Cui, L.-Z. Gong, A.-Q. Mi, Y.-Z. Jiang, Y.-D. Wu, *Proc. Natl. Acad. Sci.* **2004**, 101, 5755–5760.
- 18 Z. Tang, Z.-H. Yang, L.-F. Cun, L.-Z. Gong, A.-Q. Mi, Y.-Z. Jiang, *Org. Lett.* **2004**, 6, 2285–2287.
- 19 (a) M. Nakadai, S. Saito, H. Yamamoto, *Tetrahedron* **2002**, 58, 8167–8177; (b) N. Mase, F. Tanaka, C. F. Barbas III, *Angew. Chem., Int. Ed.* **2004**, 43, 2420–2423.
- 20 (a) H. Torii, M. Nakadai, K. Ishihara, S. Saito, H. Yamamoto, *Angew. Chem., Int. Ed.* **2004**, 43, 1983–1986; (b) A. Hartikka, P. I. Arvidsson, *Tetrahedron Asymmetry* **2004**, 15, 1831–1834.
- 21 T. Ooi, M. Taniguchi, M. Kameda, K. Maruoka, *Angew. Chem., Int. Ed.* **2002**, 41, 4542–4544.
- 22 M. Shibasaki, M. Kanai, K. Funabashi, *Chem. Commun.* **2002**, 1989–1999 and references therein.
- 23 For pioneering applications of proline as catalyst in intramolecular aldol reactions, see: (a) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, 39, 1615–1621; (b) U. Eder, G. Sauer, R. Wiechert, *Angew. Chem., Int. Ed. Engl.* **1971**, 10, 496–497.
- 24 For reviews, see: (a) B. List, *Synlett* **2001**, 1675–1686; (b) H. Gröger, J. Wilken, *Angew. Chem., Int. Ed.* **2001**, 40, 529–532; (c) B. List, *Tetrahedron* **2002**, 58, 5573–5590; (d) M. Movassaghi, E. N. Jacobsen, *Science* **2002**, 298, 1904–1905.
- 25 (a) S. Bahmanyar, K. N. Houk, *J. Am. Chem. Soc.* **2001**, 123, 11273–11283; (b) L. Hoang, S. Bahmanyar, K. N. Houk, B. List, *J. Am. Chem. Soc.*, **2003**, 125, 16–17; (c) S. Bahmanyar, K. N. Houk, H. J. Martin, B. List, *J. Am. Chem. Soc.*, **2003**, 125, 2475–2479; (d) B. List, L. Hoang, H. J. Martin, *Proc. Natl. Acad. Sci.* **2004**, 101, 5839–5842.
- 26 B. Alcaide, P. Almendros, *Angew. Chem., Int. Ed.* **2003**, 42, 858–860.
- 27 (a) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.*, **2002**, 124, 6798–6799. For a commentary, see: (b) D. F. Cauble, Jr., M. J. Krische, *Chemtracts-Org. Chem.* **2002**, 15, 380–383.
- 28 C. Pidathala, L. Hoang, N. Vignola, B. List, *Angew. Chem., Int. Ed.* **2003**, 42, 2785–2788.
- 29 (a) A. B. Northrup, I. K. Mangion, F. Hettche, D. W. C. MacMillan, *Angew. Chem., Int. Ed.* **2004**, 43, 2152–2154. See also: (b) A. B. Nortrup, D. W. C. MacMillan, *Science*, **2004**, 305, 1752–1755; (c) N. S. Chowdari, D. B. Ramachary, A. Córdova, C. F. Barbas III, *Tetrahedron Lett.*, **2002**, 43, 9591–9595.
- 30 D. F. Cauble, J. D. Gipson, M. J. Krische, *J. Am. Chem. Soc.*, **2003**, 125, 1110–1111.
- 31 (a) S. J. Taylor, M. O. Duffey, J. P. Morken, *J. Am. Chem. Soc.*, **2000**,

122, 4528–4529; (b) C.-X. Zhao, M. O. Duffey, S. J. Taylor, J. P. Morken, *Org. Lett.* **2001**, 3, 1829–1831; (c) A. E. Russell, N. O. Fuller, S. J. Taylor, P. Aurrisset, J. P. Morken, *Org. Lett.* **2004**, 6, 2309–2312.

References and Notes to Section 1.1.3.2

- 1 (a) I. Ojima (Ed.), *Catalytic Asymmetric Synthesis*, 2nd ed., Wiley: New York, **2000**; (b) E. N. Jacobsen, A. Pfaltz, H. Yamamoto (Eds.), *Comprehensive Asymmetric Catalysis*, Springer: Berlin, **1999**; Vol. 3; (c) N. Krause, A. Hoffmann-Röder, *Synthesis* **2001**, 171–196; (d) M. P. Sibi, S. Manyem, *Tetrahedron* **2000**, 56, 8033–8061.
- 2 B. Långström, G. Bergson, *Acta Chem. Scand.* **1973**, 27, 3118–3119.
- 3 (a) H. Wynberg, R. Helder, *Tetrahedron Lett.* **1975**, 16, 4057–4060; (b) K. Hermann, H. Wynberg, *J. Org. Chem.* **1979**, 44, 2238–2244.
- 4 For selected examples: (a) Y. Tamai, A. Kamifuku, E. Koshiishi, S. Miyano, *Chem. Lett.* **1995**, 957–958; (b) H. Sasai, E. Emori, T. Arai, M. Shibasaki, *Tetrahedron Lett.* **1996**, 37, 5561–5564; (c) H. Brunner, B. Hammer, *Angew. Chem., Int. Ed. Engl.* **1984**, 23, 312–313; (d) G. Desimoni, G. Dusi, G. Faita, P. Quadrelli, P. Righetti, *Tetrahedron* **1995**, 51, 4131–4144; (e) J. Christoffers, U. Rößler, T. Werner, *Eur. J. Org. Chem.* **2000**, 701–705; (f) T. Suzuki, T. Torii, *Tetrahedron: Asymmetry* **2001**, 12, 1077–1081; (g) S. Kobayashi, K. Kakumoto, Y. Mori, K. Manabe, *Israel J. Chem.* **2001**, 41, 247–249; (h) M. Nakajima, S. Yamamoto, Y. Yamaguchi, S. Nakamura, S. Hashimoto, *Tetrahedron* **2003**, 59, 7307–7313; (i) T. Ooi, T. Miki, M. Taniguchi, M. Shiraishi, M. Takeuchi, K. Maruoka, *Angew. Chem., Int. Ed.* **2003**, 42, 3796–3798.
- 5 (a) Y. Hamashima, D. Hotta, M. Sodeoka, *J. Am. Chem. Soc.* **2002**, 124, 11240–11241; (b) Y. Hamashima, H. Takano, D. Hotta, M. Sodeoka, *Org. Lett.* **2003**, 5, 3225–3228; (c) Y. Hamashima, M. Sodeoka, *Chem. Rec.* **2004**, 4, 231–242.
- 6 (a) M. Kanai, M. Shibasaki, *Asymmetric Michael Reactions*, in: *Catalytic Asymmetric Synthesis*, 2nd ed.; I. Ojima, (Ed.), Wiley: New York, **2000**, pp 569–592; (b) T. Arai, H. Sasai, K. Ae, K. Okamura, T. Date, M. Shibasaki, *Angew. Chem., Int. Ed. Engl.* **1996**, 35, 104–106; (c) Y. Xu, K. Ohori, T. Ohshima, M. Shibasaki, *Tetrahedron* **2002**, 58, 2585–2588; (d) K. Yamada, T. Arai, H. Sasai, M. Shibasaki, *J. Org. Chem.* **1998**, 63, 3666–3672.
- 7 (a) M. Sawamura, H. Hamashima, Y. Ito, *J. Am. Chem. Soc.* **1992**, 114, 8295–8296; (b) M. Sawamura, H. Hamashima, Y. Ito, *Bull. Chem. Soc. Jpn.* **2000**, 73, 2559–2562, and references therein. See also, (c) K. Takenaka, Y. Uozumi, *Org. Lett.* **2004**, 6, 1833–1835, and references therein.
- 8 Y. Mizuho, N. Kasuga, S. Komiya, *Chem. Lett.* **1991**, 2127–2130.
- 9 (a) D. J. Cram, G. D. Y. Sogah, *J. Chem. Soc., Chem. Commun.* **1981**, 625–628. See also, (b) L. Töke, L. Fenichel, M. Albert, *Tetrahedron Lett.* **1995**, 36, 5951–5954, and references therein.
- 10 (a) R. S. E. Conn, A. V. Lovell, S. Karady, L. M. Weinstock, *J. Org. Chem.* **1986**, 51, 4710–4711; (b) W. Nierinckx, M. Vandewalle, *Tetrahedron: Asymmetry*, **1990**, 1, 265–276.
- 11 For examples: (a) V. Annamalai, E. F. DiMauro, P. J. Carroll, M. C. Kozlowski, *J. Org. Chem.* **2003**, 68, 1973–1981, and references therein; (b) N. Prabakaran, G. Sundararajan, *Tetrahedron: Asymmetry*, **2002**, 13, 1053–1058; (c) S. C. Jha, N. N. Joshi, *Tetrahedron: Asymmetry*, **2001**, 12, 2463–2466; (d) S. Narasimhan, S. Velmathi, R. Balakumar, V. Radhakrishnan, *Tetrahedron Lett.* **2001**, 42, 719–721.
- 12 (a) M. Watanabe, K. Murata, T. Ikariya, *J. Am. Chem. Soc.* **2003**, 125, 7508–7509; (b) T. Ikariya, H. Wang, M. Watanabe, K. Murata, *J. Organomet. Chem.* **2004**, 689, 1377–1381.
- 13 (a) M. Yamaguchi, T. Shiraishi, M. Hirama, *Angew. Chem., Int. Ed. Engl.* **1993**, 32, 1176–1178; (b) M. Yamaguchi,

- T. Shiraishi, M. Hirama, *J. Org. Chem.* **1996**, 61, 3520–3530, and references therein.
- 14 (a) E. J. Corey, M. C. Noe, F. Xu, *Tetrahedron Lett.* **1998**, 39, 5347–5350. For other recent examples: (b) T. Ishikawa, Y. Araki, T. Kumamoto, H. Seki, K. Fukuda, T. Isobe, *Chem. Commun.* **2001**, 245–246; (c) S. Arai, R. Tsuji, A. Nishida, *Tetrahedron Lett.* **2002**, 43, 9535–9537; (d) T. Shibuguchi, Y. Fukuta, Y. Akachi, A. Sekine, T. Ohshima, M. Shibasaki, *Tetrahedron Lett.* **2002**, 43, 9539–9543; (e) T. Akiyama, M. Hara, K. Fuchibe, S. Sakamoto, K. Yamaguchi, *Chem. Commun.* **2003**, 1734–1735.
 - 15 S. Harada, N. Kumagai, T. Kinoshita, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, 125, 2582–2590.
 - 16 O. Andrey, A. Alexakis, G. Bernardinelli, *Org. Lett.* **2003**, 5, 2559–2561. See also, N. Mase, R. Thayumanavan, F. Tanaka, C. F. Barbas III, *Org. Lett.* **2004**, 6, 2527–2530, and references therein.
 - 17 (a) Y. S. Kim, S. Matsunaga, J. Das, A. Sekine, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.* **2000**, 122, 6506–6507; (b) S. Matsunaga, T. Ohshima, M. Shibasaki, *Adv. Synth. Catal.* **2002**, 344, 3–15.
 - 18 (a) N. Halland, P. S. Aburel, K. A. Jørgensen, *Angew. Chem., Int. Ed.* **2003**, 42, 661–665; (b) N. Halland, P. S. Aburel, K. A. Jørgensen, *Angew. Chem., Int. Ed.* **2004**, 43, 1272–1277, and references therein.
 - 19 M. S. Taylor, E. N. Jacobsen, *J. Am. Chem. Soc.* **2003**, 125, 11204–11205.
 - 20 N. Halland, T. Velgaard, K. A. Jørgensen, *J. Org. Chem.* **2003**, 68, 5067–5074.
 - 21 (a) P. Bakó, Z. Bajor, L. Töke, *J. Chem. Soc., Perkin Trans. 1*, **1999**, 3651–3655; (b) S. Hanessian, V. Pham, *Org. Lett.* **2000**, 2, 2975–2978; (c) E. J. Corey, F.-Y. Zhang, *Org. Lett.* **2000**, 2, 4257–4259; (d) K. Itoh, S. Kanemasa, *J. Am. Chem. Soc.* **2002**, 124, 13394–13395; (e) K. Itoh, Y. Oderaotoshi, S. Kanemasa, *Tetrahedron: Asymmetry*, **2003**, 14, 635–639.
 - 22 D. M. Barnes, J. Ji, M. G. Fickes, M. A. Fitzgerald, S. A. King, H. E. Morton, F. A. Plagge, M. Preskill, S. H. Wagaw, S. J. Wittenberger, J. Zhang, *J. Am. Chem. Soc.* **2002**, 124, 13097–13105.
 - 23 T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, 125, 12672–12673.
 - 24 F.-Y. Zhang, E. J. Corey, *Org. Lett.* **2000**, 2, 1097–1100.
 - 25 Review: M. Bandini, A. Melloni, A. Umani-Ronchi, *Angew. Chem., Int. Ed.* **2004**, 43, 550–556.
 - 26 M. S. Kerr, J. Read de Alaniz, T. Rovis, *J. Am. Chem. Soc.* **2002**, 124, 10298–10299.

References and Notes to Section 1.1.3.3

- 1 The first example of the application of the Mannich reaction to natural product synthesis is attributed to Robinson in his synthesis of tropinone; R. Robinson, *J. Chem. Soc.* **1917**, 762.
- 2 Excellent reviews see:
 - (a) E. F. Kleinmann, In *Comprehensive Organic Synthesis*; B. M. Trost, I. Fleming, Eds.; Pergamon Press: New York, 1991; Vol. 2, Chapter 4.1;
 - (b) M. Arend, B. Westerman, N. Risch, *Angew. Chem. Int. Ed.* **1998**, 37, 1044;
 - (c) S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, 99, 1069; (d) S. Denmark, O. J.-C. Nicaise, In *Comprehensive Asymmetric Catalysis*; E. N. Jacobsen, A. Pfaltz, H. Yamamoto, Eds.; Springer: Berlin, 1999, Vol. 2, 93; (e) For examples, see: *Enantioselective Synthesis of β -Amino Acids*, E. Juaristi, Ed.; Weinheim, 1997.
- 3 (a) D. Seebach, M. Hoffmann, *Eur. J. Org. Chem.* **1998**, 1337; (b) Y. Aoyagi, R. P. Jain, R. M. Williams, *J. Am. Chem. Soc.* **2001**, 123, 3472 and references therein; (c) U. Schöllkopf, in *Topics in Current Chemistry*, F. L. Boschke, Ed., Springer Verlag: Berlin, 1983; Vol. 109, pp 45–85; (d) D. A. Evans, F. Urpi, T. C. Somers, J. S. Clark, M. T. Bilodeau, *J. Am. Chem. Soc.* **1990**, 112, 8215; (e) R. Kober, K. Papadopoulos, W. Miltz, D. Enders, W. Steglich, H. Reuter, H. Puff, *Tetrahedron* **1985**, 42, 1963; (f) C. Palomo, M. Oiarbide, A. Landa, M. C. Gonzales-Rego, J. M. Garcia, A. Gonzales, J. M. Odriozola, M. Martin-Pastor, A. Linden, *J. Am. Chem. Soc.* **2002**, 124, 8637 and references therein.

- 4 (a) H. Ishitani, M. Ueno, S. Kobayashi, *J. Am. Chem. Soc.* **1997**, 119, 7153; (b) S. Kobayashi, T. Hamada, K. Manabe, *J. Am. Chem. Soc.* **2002**, 124, 5640; (c) H. Ishitani, S. Ueno, S. Kobayashi, *J. Am. Chem. Soc.* **2000**, 122, 8180.
- 5 (a) E. Hagiwara, A. Fujii, M. Sodeoka, *J. Am. Chem. Soc.* **1998**, 120, 2474; (b) A. Fujii, E. Hagiwara, M. Sodeoka, *J. Am. Chem. Soc.* **1999**, 121, 545.
- 6 (a) D. Ferraris, B. Young, T. Dudding, T. Lectka, *J. Am. Chem. Soc.* **1998**, 120, 4548; (b) D. Ferraris, B. Young, C. Cox, T. Dudding, W. J. Drury III, L. Ryzhkov, T. Taggi, T. Lectka, *J. Am. Chem. Soc.* **2002**, 124, 67 and references therein.
- 7 A. G. Wenzel, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, 124, 12964.
- 8 T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem. Int. Ed.* **2004**, 43, 1566.
- 9 N. Josephsohn, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **2004**.
- 10 B. M. Trost, *Science* **1991**, 254, 1471.
- 11 See: M. Shibasaki, H. Sasai, T. Arai, *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 1236. and references therein.
- 12 (a) N. Yoshikawa, Y. M. A. Yamada, J. Das, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1999**, 121, 4168; (b) N. Yoshikawa, N. Kumagai, S. Matsunaga, G. Moll, G.; T. Ohshima, T. Suzuki, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, 123, 2466; (c) D. Sawada, M. Shibasaki, *Angew. Chem. Int. Ed.* **2000**, 39, 209.
- 13 S. Yamasaki, T. Iida, M. Shibasaki, *Tetrahedron Lett.* **1999**, 40, 307.
- 14 S. Matsunaga, N. Kumagai, N. Harada, S. Harada, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, 125, 4712.
- 15 S. Matsunaga, T. Yoshida, H. Morimoto, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2004**, 126, 8777.
- 16 (a) S. Matsunaga, J. Das, J. Roels, E. M. Vogel, N. Yamamoto, T. Iida, K. Yamaguchi, M. Shibasaki, *J. Am. Chem. Soc.* **2000**, 122, 2252; (b) N. Kumagai, S. Matsunaga, T. Kinoshita, S. Harada, S. Okada, S. Sakamoto, K. Yamaguchi, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, 125, 2169. and references therein; (c) S. Harada, N. Kumagai, T. Kinoshita, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, 125, 2582 and references therein.
- 17 (a) B. M. Trost, H. Ito, *J. Am. Chem. Soc.* **2000**, 122, 12003; (b) B. M. Trost, H. Ito, E. Silcoff, *J. Am. Chem. Soc.* **2001**, 123, 3367; (c) B. M. Trost, E. Silcoff, H. Ito, *Org. Lett.* **2001**, 3, 2497.
- 18 B. M. Trost, L. M. Terrell, *J. Am. Chem. Soc.* **2003**, 125, 338.
- 19 (a) K. Juhl, N. Gathergood, K. A. Jørgensen, *Chem. Commun.* **2000**, 2211; (b) K. Juhl, K. A. Jørgensen, *J. Am. Chem. Soc.* **2002**, 124, 2420.
- 20 K. Juhl, N. Gathergood, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2001**, 40, 2995.
- 21 For reviews of C₂-bisoxazoline-Lewis acid complexes see: (a) J. S. Johnson, D. A. Evans, *Acc. Chem. Res.* **2000**, 33, 325; (b) K. A. Jørgensen, M. Johannsen, S. Yao, H. Audrain, J. Thorhauge, *Acc. Chem. Res.* **1999**, 32, 605.
- 22 M. Marigo, A. Kjaersgaard, K. Juhl, N. Gathergood, K. A. Jørgensen, *Chem. Eur. J.* **2003**, 9, 2395.
- 23 (a) P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2001**, 40, 3726; (b) B. List, *Tetrahedron* **2002**, 58, 5573; (c) J. Gröger, J. Wilken, *Angew. Chem. Int. Ed.* **2001**, 40, 529; (d) E. R. Jarvo, S. J. Miller, *Tetrahedron* **2002**, 58, 2481; (e) R. O. Duthaler, *Angew. Chem. Int. Ed.* **2003**, 42, 975.
- 24 (a) Z. G. Hajos, D. R. Parrish, Asymmetric Synthesis of Optically Active Polycyclic Organic Compounds. German Patent. D. E. 2102623, Jul 29, 1971; (b) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, 39, 1615; (c) U. Eder, G. Sauer, R. Wiechert, Optically Active 1,5-Indanone and 1,6-Naphthalenedione. German Patent DE 2014757, Oct 7, 1971; (d) U. Eder, G. Sauer, R. Wiechert, *Angew. Chem. Int. Ed.* **1971**, 10, 496; (e) C. Agami, *Bull. Soc. Chim. Fr.* **1988**, 499.
- 25 For example, the total synthesis of Taxol: S. J. Danishefsky, et al. *J. Am. Chem. Soc.* **1996**, 118, 2843.
- 26 (a) B. List, *J. Am. Chem. Soc.* **2000**, 122, 9336; (b) B. List, P. Porjalev, W. T. Biller, H. J. Martin, *J. Am. Chem. Soc.* **2002**, 124, 827.
- 27 (a) B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, 122, 2395;

- (b) W. Notz, B. List, *J. Am. Chem. Soc.* **2000**, *122*, 7386.
- 28 K. Manabe, S. Kobayashi, *Org. Lett.* **1999**, *1*, 1965. and references therein.
- 29 W. Notz, K. Sakthivel, T. Bui, G. Zhong, C. F. Barbas III, C. F. *Tetrahedron Lett.* **2001**, *42*, 199.
- 30 K. Sakthivel, W. Notz, T. Bui, C. F. Barbas III, *J. Am. Chem. Soc.* **2001**, *123*, 5260.
- 31 T. Bui, C. F. Barbas III, *Tetrahedron Lett.* **2000**, *41*, 6951.
- 32 (a) A. E. Taggi, A. M. Hafez, T. Lectka, *Acc. Chem. Res.* **2002**, *36*, 10; (b) S. Yao, M. Johannsen, R. G. Hazell, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **1998**, *37*, 3121.
- 33 A. Córdova, W. Notz, G. Zhong, J. M. Betancort, C. F. Barbas III, *J. Am. Chem. Soc.* **2002**, *124*, 1844.
- 34 I. Ibrahim, J. Casas, A. Córdova, *Angew. Chem.* **2004**, *43*, 6528.
- 35 T. Itoh, M. Yokoya, K. Miyauchi, K. Nagata, A. Ohsawa, *Org. Lett.* **2003**, *5*, 4301.
- 36 (a) A. Córdova, W. Notz, C. F. Barbas III, *J. Org. Chem.* **2002**, *67*, 301; (b) A. Bøgevig, N. Kumaragurubaran, K. A. Jørgensen, *Chem. Commun.* **2002**, 620; (c) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 6798; (b) N. S. Chowdari, D. B. Ramachary, A. Córdova, C. F. Barbas III, *Tetrahedron Lett.* **2002**, *43*, 9591; (c) A. Córdova, W. Notz, C. F. Barbas III, *Chem. Commun.* **2002**, 67, 3034; (d) A. Bøgevig, K. Juhl, N. Kumaragurubaran, W. Zhuang, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2002**, *41*, 1790; (e) B. List, *J. Am. Chem. Soc.* **2002**, *124*, 5656.
- 37 T. D. Machajewski, C. -H. Wong, *Angew. Chem. Int. Ed.* **2000**, *39*, 1352. and references therein.
- 38 A. Córdova, S. Watanabe, F. Tanaka, W. Notz, C. F. Barbas III, *J. Am. Chem. Soc.* **2002**, *124*, 1866.
- 39 (a) A. Córdova, 225th ACS National Meeting, New Orleans, LA. Amine-Catalyzed Direct Asymmetric Mannich-type Reactions: Enantioselective Synthesis of Amino acid and Amino Alcohol Derivatives; (b) A. Córdova, *Synlett.* **2003**, 1651; (c) A. Córdova, *Chem. Eur. J.* **2004**, *10*, 1987.
- 40 The Mannich adducts are reduced to the more stable γ -amino alcohols prior to isolation and ee determination due to their lower risk of decomposition, epimerization and racemization.
- 41 I. Ibrahim, J. Samec, J.-E. Bäckvall, A. Córdova, *Tetrahedron Lett.* **2005**, *46*, 3941.
- 42 (a) S.-i. Watanabe, A. Córdova, F. Tanaka, C. F. Barbas III, *Org. Lett.* **2002**, *4*, 4519; (b) A. Córdova, C. F. Barbas III, *Tetrahedron Lett.* **2003**, *44*, 1923.
- 43 V. Vinkovic, V. Sunjic, *Tetrahedron* **1997**, *53*, 689
- 44 A. Córdova, C. F. Barbas III, *Tetrahedron Lett.* **2002**, *43*, 7749.
- 45 W. Zhuang, S. Saaby, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2004**, *43*, 4476.
- 46 D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356.

References and Notes to Section 1.1.4

- W. J. de Klein, in *Organic Synthesis by Oxidation with Metal Compounds*, (Eds: W. J. Mijs, C. R. H. de Jonge), Plenum Press, New York, **1986**, pp 261–314.
- Sh. O. Badanyan, G. G. Melikyan, D. A. Mkrtchyan, *Russ. Chem. Rev.* **1989**, *58*, 286–296; *Uspekhi Khimii* **1989**, *58*, 475–495.
- G. G. Melikyan, *Synthesis*, **1993**, 833–850.
- J. Iqbal, B. Bhatia, N. K. Nayyar, *Chem. Rev.* **1994**, *94*, 519–564.
- B. B. Snider, *Chem. Rev.* **1996**, *96*, 339–363.
- (a) G. G. Melikyan, *Organic Reactions* **1997**, *49*, 427–675; (b) G. G. Melikyan, *Aldrichim. Acta* **1998**, *31*, 50–64.
- S. A. Kates, M. A. Dombroski, B. B. Snider, *J. Org. Chem.* **1990**, *55*, 2427–2436.
- B. B. Snider, R. B. Smith, *Tetrahedron*, **2002**, *58*, 25–34.
- B. B. Snider, Q. Che, *Tetrahedron* **2002**, *58*, 7821–7827.
- B. A. M. Cole, L. Han, B. B. Snider, *J. Org. Chem.* **1996**, *51*, 7832–7847.

- 11 D. P. Curran, T. M. Morgan, C. E. Schwartz, B. B. Snider, M. A. Dombroski *J. Am. Chem. Soc.* **1991**, *113*, 6607–6617.
- 12 M. A. Dombroski, S. A. Kates, B. B. Snider, *J. Am. Chem. Soc.* **1990**, *112*, 2759–2767.
- 13 (a) P. A. Zoretic, M. Wang, Y. Zhang, Z. Shen, A. A. Ribeiro, *J. Org. Chem.* **1996**, *61*, 1806–1813; (b) P. A. Zoretic, Y. Zhang, H. Fang, A. A. Ribeiro, *J. Org. Chem.* **1998**, *63*, 1162–1167; (c) P. A. Zoretic, H. Fang, A. A. Ribeiro, *J. Org. Chem.* **1998**, *63*, 4779–4785; (d) P. A. Zoretic, H. Fang, A. A. Ribeiro, *J. Org. Chem.* **1998**, *63*, 7213–7217.
- 14 B. B. Snider, J. Y. Kiseligof, B. M. Foxman *J. Org. Chem.* **1998**, *63*, 7945–7952.
- 15 (a) E. I. Heiba, R. M. Dessau, *J. Am. Chem. Soc.* **1971**, *93*, 524; (b) E. I. Heiba, R. M. Dessau, *J. Am. Chem. Soc.* **1972**, *94*, 2888.
- 16 B. B. Snider, T. Kwon, *J. Org. Chem.* **1990**, *55*, 1965–1968.
- 17 (a) M. G. Vinogradov, V. I. Dolinko, G. I. Nikishin, *Bull. Acad. Sci. USSR, Ser. Chem.* **1984**, *33*, 334–341; *Chem. Abstr.* **1984**, *100*, 209194u; (b) M. G. Vinogradov, V. I. Dolinko, G. I. Nikishin, *Bull. Acad. Sci. USSR, Ser. Chem.* **1984**, *33*, 1884–1887; *Chem. Abstr.* **1985**, *102*, 166306d.
- 18 I. Ryu, H. Alper *J. Am. Chem. Soc.* **1993**, *115*, 7543–7544.
- 19 (a) R. Kumabe, H. Nishino *Tetrahedron Lett.* **2004**, *45*, 703–706; (b) T. Yamada, Y. Iwahara, H. Nishino, K. Kurosawa *J. Chem. Soc., Perkin Trans. 1* **1993**, 609–616.
- 20 B. B. Snider, J. R. Duvall *Org. Lett.* **2004**, *6*, 1265–1268.
- 21 (a) D. Yang, X.-Y. Ye, M. Xu, K.-W. Pang, N. Zou, R. M. Lechter *J. Org. Chem.* **1998**, *63*, 6446–6447; (b) D. Yang, X.-Y. Ye, S. Gu, M. Xu *J. Am. Chem. Soc.* **1999**, *121*, 5579–5580; (c) D. Yang, X.-Y. Ye, M. Xu, K.-W. Pang, K.-K. Cheung *J. Am. Chem. Soc.* **2000**, *122*, 1658–1663; (d) D. Yang, X.-Y. Ye, M. Xu *J. Org. Chem.* **2000**, *65*, 2208–2217; (e) D. Yang, M. Xu, M.-Y. Bian *Org. Lett.* **2001**, *3*, 111–114.
- 22 B. B. Snider, J. E. Merritt, M. A. Dombroski, B. O. Buckman, *J. Org. Chem.* **1991**, *56*, 5544–5553.
- 23 B. B. Snider, R. M. Mohan, S. A. Kates *J. Org. Chem.* **1985**, *50*, 3659–3661.
- 24 R. Mohan, S. A. Kates, M. A. Dombroski, B. B. Snider, *Tetrahedron Lett.* **1987**, *28*, 845–848.
- 25 Q. Zhang, R. M. Mohan, L. Cook, S. Kazanis, D. Peisach, B. M. Foxman, B. B. Snider, *J. Org. Chem.* **1993**, *58*, 7640–7651.
- 26 B. B. Snider, R. M. Mohan, S. A. Kates, *Tetrahedron Lett.* **1987**, *28*, 841–844.
- 27 B. B. Snider, Q. Zhang, M. A. Dombroski, *J. Org. Chem.* **1992**, *57*, 4195–4205.
- 28 B. B. Snider, Q. Zhang, *J. Org. Chem.* **1993**, *58*, 3185–3187.
- 29 B. B. Snider, J. J. Patricia, *J. Org. Chem.* **1989**, *54*, 38–46.
- 30 B. B. Snider, J. J. Patricia, S. A. Kates, *J. Org. Chem.* **1988**, *53*, 2137–2143.
- 31 B. Snider, B. A. McCarthy, *Tetrahedron* **1993**, *49*, 9447–9452.
- 32 E. J. Corey, A. W. Gross, *Tetrahedron Lett.* **1985**, *26*, 4291–4294.
- 33 N. Fujimoto, H. Nishino, K. Kurosawa, *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3161–3168.

References and Notes to Section 1.1.5

- 1 (a) A. L. J. Beckwith, *Chem. Soc. Rev.* **1993**, *22*, 143–151; (b) A. L. J. Beckwith, C. J. Easton, *J. Am. Chem. Soc.* **1981**, *103*, 615–619; (c) A. L. J. Beckwith, A. Z. Zavitsas, *J. Am. Chem. Soc.* **1995**, *117*, 607–614; (d) V. Malatesta, K. U. Ingold, *J. Am. Chem. Soc.* **1981**, *103*, 609–614; (e) V. Malatesta, J. C. Scaiano, *J. Org. Chem.* **1982**, *47*, 1455–1459; (f) W. K. Busfield, I. D. Grice, I. D. Jenkins, *J. Chem. Soc., Perkin Trans. 2*, **1994**, 1079–1086; (g) W. K. Busfield, I. D. Grice, I. D. Jenkins, M. J. Monteiro, *J. Chem. Soc., Perkin Trans. 2*, **1994**, 1071–1077; (h) J. M. Tedder, *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 401–410; (i) B. P. Roberts, *Chem. Soc. Rev.* **1999**, *28*, 25–35; (j) H.-S. Dang, B. P. Roberts, D. A. Tocher, *J. Chem. Soc., Perkin Trans.*

- 1, 2001, 2452–2461; (k) A. B. Shtarev, F. Tian, W. R. Dolbier, Jr., B. E. Smart, *J. Am. Chem. Soc.* **1999**, 121, 7335–7341; (l) L. Feray, N. Kuznetsov, P. Renaud, In *Radicals in Organic Synthesis*; P. Renaud, M. P. Sibi, Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2, pp 246–278.
- 2 The efficiency of hydrogen atom abstraction is often influenced by several factors involving thermodynamic, polar, stereoelectronic and steric effects. For instance, C–H bonds α to oxygen are not always susceptible to abstraction when nucleophilic radical initiators are used. P. Kaushal, P. L. H. Mok, B. P. Roberts, *J. Chem. Soc., Perkin Trans. 2*, **1990**, 1663–1670.
- 3 Pioneering studies in this area include (a) R. L. Jacobs, G. G. Ecke, *J. Org. Chem.* **1963**, 28, 3036–3038; (b) J. Dieckmann, C. J. Pedersen, *J. Org. Chem.* **1963**, 28, 2879–2880; (c) D. Elad, R. D. Youssefeyeh, *J. Org. Chem.* **1964**, 29, 2031–2032; (d) I. Rosenthal, D. Elad, *Tetrahedron* **1967**, 23, 3193–3204; (e) H. Muramatsu, K. Inukai, T. Ueda, *J. Org. Chem.* **1964**, 29, 2220–2223; (f) A. Citterio, A. Arnoldi, A. Griffini, *Tetrahedron* **1982**, 38, 393–395; (g) D. P. Matthews, J. R. McCarthy, *J. Org. Chem.* **1990**, 55, 2973–2975; (h) F. Minisci, A. Citterio, E. Vismara, C. Giordano, *Tetrahedron*, **1985**, 41, 4157–4170; (i) R. H. Crabtree, *Pure Appl. Chem.* **1995**, 67, 39–45; (j) S. H. Brown, R. H. Crabtree, *J. Am. Chem. Soc.* **1989**, 111, 2935–2946. Reviews containing a brief discussion on this topic: (k) C. Walling, E. S. Huyser, *Org. React.* **1963**, 13, 91–149; (l) P. I. Abell, In *Free Radicals*; J. K. Kochi, Ed.; Wiley-Interscience: New York, 1973; Vol. 2; p 63; (m) B. Giese, *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Pergamon Press: Oxford, 1986.
- 4 (a) C. Walling, In *Active Oxygen in Chemistry*; C. S. Foote, J. S. Valentine, A. Greenberg, J. F. Liebman, Eds.; Blackie Academic Professional: New York, 1995; pp 29; (b) A. Bravo, F. Fontana, G. Fronza, F. Minisci, *J. Org. Chem.* **1998**, 63, 254–263; (c) H. Seto, K. Yoshida, S. Yoshida, T. Shimizu, H. Seki, M. Hoshino, *Tetrahedron Lett.* **1996**, 37, 4179–4182. Radical hydroxylation of ethereal C–H bonds occurs but through one-electron transfer from oxygen lone pair to oxo metal species and subsequent proton elimination, see (d) T. Katsuki, In *Radicals in Organic Synthesis*; P. Renaud, M. P. Sibi, Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2, pp 113–126.
- 5 For instance, see (a) E. Vilsmaier, *Liebigs Ann. Chem.* **1969**, 728, 12–16; (b) C. G. Kruse, N. L. J. M. Broekhof, A. van der Gen, *Tetrahedron Lett.* **1976**, 1725–1728. Also see, (c) R. Baati, A. Valleix, C. Mioskowski, D. K. Barma, J. R. Falck, *Org. Lett.* **2000**, 2, 485–487; (d) M. Ochiai, T. Sueda, *Tetrahedron Lett.* **2004**, 45, 3557–3559; (e) J. M. Barks, B. C. Gilbert, A. F. Parsons, B. Upeandran, *Tetrahedron Lett.* **2000**, 41, 6249–6252; (f) A. Inoue, H. Shinokubo, K. Oshima, *Synlett* **1999**, 1582–1584.
- 6 Radical translocation, an indirect method for the C–H transformation of ethers, has also been developed; (a) J. Robertson, J. Pillai, R. K. Lush, *Chem. Soc. Rev.* **2001**, 30, 94–103; (b) D. P. Curran, D. Kim, H. T. Liu, W. Shen, *J. Am. Chem. Soc.* **1988**, 110, 5900–5902; (c) D. Denenmark, P. Hoffmann, T. Winkler, A. Waldner, A. D. Mesmaeker, *Synlett*, **1991**, 621–624.
- 7 (a) J. Gong, P. L. Fuchs, *J. Am. Chem. Soc.* **1996**, 118, 4486–4487; (b) J. Xiang, P. L. Fuchs, *J. Am. Chem. Soc.* **1996**, 118, 11986–11987; (c) J. Xiang, W. Jiang, J. Gong, P. L. Fuchs, *J. Am. Chem. Soc.* **1997**, 119, 4123–4129 and references therein.
- 8 K. Hirao, S. Sakaguchi, Y. Ishii, *Tetrahedron Lett.* **2002**, 43, 3617–3620.
- 9 S. Kim, N. Kim, W.-J. Chung, C. H. Cho, *Synlett* **2001**, 937–940.
- 10 (a) M. Fernandez, R. Alonso, *Org. Lett.* **2003**, 5, 2461–2464; (b) S. Torrente, R. Alonso, *Org. Lett.* **2001**, 3, 1985–1987.
- 11 T. Yoshimitsu, M. Tsunoda, H. Nagaoka, *Chem. Commun.* **1999**, 1745–1746.
- 12 T. Yoshimitsu, Y. Arano, H. Nagaoka, *J. Org. Chem.* **2003**, 68, 625–627.
- 13 (a) K. Yamada, H. Fujihara, Y. Yamamoto, Y. Miwa, Y. Taga,

- K. Tomioka, *Org. Lett.* **2002**, 4, 3509–3511; (b) K. Yamada, Y. Yamamoto, K. Tomioka, *Org. Lett.* **2003**, 5, 1797–1799; (c) Y. Yamamoto, K. Yamada, K. Tomioka, *Tetrahedron Lett.* **2004**, 45, 795–797; (d) K. Yamada, Y. Yamamoto, M. Maekawa, K. Tomioka, *J. Org. Chem.* **2004**, 69, 1531–1534; (e) K. Yamada, Y. Yamamoto, K. Tomioka, *J. Synth. Org. Chem. Jpn.* **2004**, 62, 1158–1165.
- 14 Recent reviews of triethylborane chemistry include: (a) C. Ollivier, P. Renaud, *Chem. Rev.* **2001**, 101, 3415–3434; (b) H. Yorimitsu, K. Oshima, In *Radicals in Organic Synthesis*; P. Renaud, M. P. Sibi, Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1, pp 11–27; (c) G. O'Mahony, *Synlett* **2004**, 572–573.
- 15 J. R. Sanderson, J. J. Lin, R. G. Duranleau, E. L. Yeakey, E. T. Marquis, *J. Org. Chem.* **1988**, 53, 2859–2861.
- 16 T. Yoshimitsu, T. Makino, H. Nagaoka, *J. Org. Chem.* **2003**, 68, 7548–7550.
- 17 T. Yoshimitsu, T. Makino, H. Nagaoka, *J. Org. Chem.* **2004**, 69, 1993–1998.
- 18 T. Yoshimitsu, Y. Arano, H. Nagaoka, *J. Org. Chem.* **2005**, 70, 2342–2345.
- 19 An intermediacy of electrophilic alkoxyl radicals (e.g., *tert*-butoxyl radical) possibly generated in the reaction mixture, which exhibit polarity matching with ethereal α -C–H bonds, may also be considered. Studies on the mechanism are in progress.
- 20 Tetrahydropyran (THP) has been found to be a poor substrate in the present α -C–H hydroxyalkylation reaction (20% yield; dr 80:20). This result seems to be related to the previous observation of the low susceptibility to hydrogen abstraction of THP. See Refs. [1e, f].
- H. Bjorsvik, *Org. Process Res. Dev.*, **1998**, 2, 261.
- 4 F. Minisci, F. Recupero, M. Rodinò, M. Sala and A. Schneider, *Org. Process Res. Dev.*, **2003**, 7, 794.
- 5 Reviews in the subject: (a) F. Minisci, F. Recupero, G. F. Pedulli and M. Lucarini, *J. Mol. Catal.*, **2003**, 204–205, 63; (b) B. Z. Zhan and A. Thompson, *Tetrahedron*, **2004**, 60, 2917; (c) T. Mollat and B. Baiker, *Chem. Rev.*, **2004**, 104, 3037; (d) R. A. Sheldon, I. W. C. E. Arends, G. S. Brink and A. Dijkstra, *Acc. Chem. Res.*, **2002**, 35, 774; (e) P. Vinke, D. de Wit, A. T. S. W. de Goede and H. van Bekkum, *Stud. Surf. Sci. Catal.*, **1992**, 72, 1.
- 6 F. Minisci, F. Recupero, A. Cecchetto, C. Gambarotti, C. Punta, R. Faletti, R. Paganelli and G. F. Pedulli, *J. Org. Chem.*, **2004**, 109.
- 7 N. Ito, S. E. Phillips, K. D. Yadav and P. F. Knowles, *J. Mol. Biol.*, **1994**, 238, 794.
- 8 B. A. Steinhoff, S. R. Fix and S. S. Stahl, *J. Am. Chem. Soc.*, **2002**, 124, 766.
- 9 A. E. S. de Noay, A. C. Besemer and H. van Bokkum, *Synthesis*, **1996**, 1153.
- 10 A. Cecchetto, F. Fontana, F. Minisci and F. Recupero, *Tetrahedron Lett.*, **2001**, 42, 6653.
- 11 F. Minisci, C. Punta, F. Recupero, F. Fontana and G. F. Pedulli, *Chem. Comm.*, **2002**, 688.
- 12 T. Iwahama, Y. Yoshino, T. Keitoku, S. Sakaguchi and Y. Ishii, *J. Org. Chem.*, **2000**, 65, 6502.
- 13 F. Minisci, O. Porta, F. Recupero, C. Gambarotti, R. Paganelli, G. F. Pedulli and F. Fontana, *Tetrahedron Lett.*, **2004**, 45, 1607.
- 14 K. P. Peterson and R. C. Larcock, *J. Org. Chem.*, **1998**, 63, 3185.
- 15 B. A. Steinhoff and S. S. Stahl, *Org. Lett.*, **2002**, 4, 4179.
- 16 J. T. Bagdanoff, E. M. Ferreira and B. M. Stoltz, *Org. Lett.*, **2003**, 5, 835.
- 17 B. Z. Zhan, M. A. White, T. K. Sham, J. A. Pincock, R. J. Doucet, K. V. R. Rao, K. N. Robertson and T. S. Cameron, *J. Am. Chem. Soc.*, **2003**, 125, 2195.
- 18 (a) N. Kakinchi, T. Nishimura, M. Inane and S. Uemura, *Bull. Soc. Chem. Jpn.*,

References to Section 1.1.6

- 1 R. C. Larock, "Comprehensive Organic transformations" pg 1234. Wiley-VCH, New York, **1999**.
- 2 B. M. Trost, J. Fleming and S. V. Ley, "Comprehensive Organic Syntheses" Vol. 7, Pergamon, Oxford, **1991**.
- 3 A. Amati, G. Dosualdo, L. Zhao, A. Bravo, F. Fontana, F. Minisci and

- 2001, 74, 165; (b) N. Kakinchi, T. Nishimura, M. Inane and S. Uemura, *Chem. Comm.*, **2000**, 1245.
- 19 F. Minisci, O. Porta, F. Recupero, C. Punta, C. Gambarotti, M. Piccinini, L. Galimberti, *Synlett.*, **2004**, in press.
- 20 S. Biella, G. Castiglioni, C. Fumagalli, L. Proti, M. Rossi, *Catal. Today*, **2002**, 72, 43.
- 21 R. Neumann, M. Levin, *J. Org. Chem.*, **1991**, 56, 5707.
- 22 M. Besson, G. Fleche, P. Fuertes, P. Gallezot, F. Lahmer, *Rec. Trav. Chim. Pays-Bas*, **1996**, 115, 217.

References and Notes to Section 1.1.7

- 1 (a) *Comprehensive Organic Synthesis*, B. M. Trost, I. Fleming (Eds.), Pergamon: Oxford, England, 1991; (b) F. A. Luzzio, *Org. React.* **1998**, 53, 1–221; (c) T. T. Tidwell, *Org. React.* **1990**, 39, 297–572.
- 2 For a recent review, see: (a) B. M. Stoltz, *Chem. Lett.* **2004**, 33, 362–367. For discussions on kinetic resolution, see: (b) V. S. Martin, S. S. Woodward, T. Katsuki, Y. Yamada, M. Ikeda, K. B. Sharpless, *J. Am. Chem. Soc.* **1981**, 103, 6237–6240; (c) C.-S. Chen, Y. Fujimoto, G. Girdaukas, C. J. Sih, *J. Am. Chem. Soc.* **1982**, 104, 7294–7299; (d) H. B. Kagan, J. C. Fiaud, in *Topics in Stereochemistry*, E. L. Eliel (Ed.), Wiley & Sons: New York, 1988, Vol. 18, pp 249–330; (e) J. M. Keith, J. F. Larrow, E. N. Jacobsen, *Adv. Synth. Catal.* **2001**, 343, 5–26.
- 3 (a) T. Nishimura, T. Onoue, K. Ohe, S. Uemura, *Tetrahedron Lett.* **1998**, 39, 6011–6014; (b) T. Nishimura, T. Onoue, K. Ohe, S. Uemura, *J. Org. Chem.* **1999**, 64, 6750–6755.
- 4 E. M. Ferreira, B. M. Stoltz, *J. Am. Chem. Soc.* **2001**, 123, 7725–7726.
- 5 D. R. Jensen, J. S. Pugsley, M. S. Sigman, *J. Am. Chem. Soc.* **2001**, 123, 7475–7476.
- 6 J. T. Bagdanoff, E. M. Ferreira, B. M. Stoltz, *Org. Lett.* **2003**, 5, 835–837.
- 7 S. K. Mandal, D. R. Jensen, J. S. Pugsley, M. S. Sigman, *J. Org. Chem.* **2003**, 68, 4600–4603.
- 8 J. T. Bagdanoff, B. M. Stoltz, *Angew. Chem., Int. Ed.* **2004**, 43, 353–357.
- 9 K. Masutani, T. Uchida, R. Irie, T. Katsuki, *Tetrahedron Lett.* **2000**, 41, 5119–5123.
- 10 R. Irie, T. Katsuki, *Chem. Rec.* **2004**, 4, 96–109.
- 11 A. T. Radosevich, C. Musich, F. D. Toste, *J. Am. Chem. Soc.* **2005**, 127, 1090–1091.
- 12 R. A. Sheldon, I. W. C. E. Arends, in *Advances in Catalytic Activation of Dioxygen by Metal Complexes*, L. I. Simandi (Ed.), Kluwer: Dordrecht, 2003, Vol. 26, Chap. 3, p 123–155.
- 13 B. A. Steinhoff, S. S. Stahl, *Org. Lett.* **2002**, 4, 4179–4181.
- 14 J. A. Mueller, M. S. Sigman, *J. Am. Chem. Soc.* **2003**, 125, 7005–7013.
- 15 (a) J. A. Mueller, D. R. Jensen, M. S. Sigman, *J. Am. Chem. Soc.* **2002**, 124, 8202–8203; (b) D. R. Jensen, M. S. Sigman, *Org. Lett.* **2003**, 5, 63–65.
- 16 S. S. Stahl, J. L. Thorman, R. C. Nelson, M. A. Kozee, *J. Am. Chem. Soc.* **2001**, 123, 7188–7189.
- 17 R. M. Trend, B. M. Stoltz, *J. Am. Chem. Soc.* **2004**, 126, 4482–4483.
- 18 R. J. Nielsen, J. M. Keith, B. M. Stoltz, W. A. Goddard, III, *J. Am. Chem. Soc.* **2004**, 126, 7967–7974.
- 19 D. D. Caspi, D. C. Ebner, J. T. Bagdanoff, B. M. Stoltz, *Adv. Synth. Catal.* **2004**, 346, 185–189.
- 20 D. C. Ebner, B. M. Stoltz, unpublished results.

References to Section 1.2.1

- 1 (a) M. Schlosser, *Pure Appl. Chem.* **1988**, 60, 1627–1634; (b) M. Schlosser, F. Faigl, L. Franzini, H. Geneste, G. Katsoulos, G.F. Zhong, *Pure Appl. Chem.* **1994**, 66, 1439–1448; (c) M. Schlosser (Ed.) Wiley, 2002; pp 1–352.
- 2 L. Lochmann, *Eur. J. Inorg. Chem.* **2000**, 1115–1126.
- 3 X. Xia, *n*-Butyllithium-potassium *t*-butoxide, in: *Handbook of Reagents for Organic Synthesis. Acidic and Basic Reagents*; H. J. Reich and J. H. Rigby (Eds.), pages 86–87, Wiley: Chichester **1999**.
- 4 M. Schlosser, M. Kotthaus, *Eur. J. Org. Chem.* **1999**, 459–462.

- 5 A. Zellner, M. Schlosser, *Synlett* **2001**, 1016–1018.
- 6 A. A. Morton, E. E. Magat, R. L. Letsinger, *J. Am. Chem. Soc.* **1947**, 69, 950–961.
- 7 C. F. Wofford, *US Patent* 3294768; **1963**.
- 8 M. Marsch, K. Harms, L. Lochmann, G. Boche, *Angew. Chem., Int. Ed. Engl.* **1990**, 29, 308–309.
- 9 A. R. Kennedy, J. G. MacLellan, R. E. Mulvey, *Angew. Chem. Int. Ed.* **2001**, 40, 3245–3247.
- 10 C.-M. Yu, W.-H. Jung, H.-S. Choi, J. Lee, J.-K. Lee, *Tetrahedron Lett.* **1995**, 36, 8255–8258.
- 11 R. Krassnig, H. Schmidhammer, K. Wurst, *Helv. Chim. Acta* **2000**, 83, 380–383.
- 12 H. C. Brown, K. S. Bhat, *J. Am. Chem. Soc.* **1986**, 108, 293–294.
- 13 W. R. Roush, R. L. Halterman, *J. Am. Chem. Soc.* **1986**, 108, 294–296.
- 14 M. Schlosser, L. Franzini, *Synthesis* **1998**, 707–709.
- 15 E. Moret, L. Franzini, M. Schlosser, *Chem. Ber./Recueil* **1997**, 130, 335–339.
- 16 J. D. Revell, A. Ganesan, *J. Org. Chem.* **2002**, 67, 6250–6252.
- 17 J. D. Revell, B. Dörner, P. White, A. Ganesan, *Org. Lett.*, **2005**, 7, 831–833.
- 18 G. Rauchschiwalbe, M. Schlosser, *Helv. Chim. Acta*, **1975**, 58, 1094–1099.
- 19 M. Schlosser, H. Bosshardt, A. Walde, M. Stähle, *Angew. Chem., Int. Ed. Engl.* **1980**, 19, 303.
- 20 F. Mongin, R. Maggi, M. Schlosser, *Chimia*, **1996**, 50, 650–652.
- 21 G. Rauchschiwalbe, A. Zellner, M. Schlosser, *Eur. J. Org. Chem.* **2001**, 3903–3909.
- 5 H. Hattori, *Chem. Rev.* **1995**, 95, 537–558.
- 6 J.-I. Take, N. Kikuchi, Y. Yoneda, *J. Catal.* **1971**, 21, 164–170.
- 7 H. Gorzawski, W. F. Hölderich, *Appl. Catal. A* **1999**, 179, 131–137.
- 8 H. Handa, Y. Fu, T. Baba, Y. Ono, *Catal. Lett.* **1999**, 59, 195–200.
- 9 K. Tanaka, H. Yanashima, M. Minobe, G. Suzukamo, *Appl. Surf. Sci.* **1997**, 121/122, 461–467.
- 10 S. V. Bordawekar, R. J. Davis, *J. Catal.* **2000**, 189, 79–90.
- 11 J. March, *Advanced Organic Chemistry*, John Wiley & Sons, 4th Ed., New York, **1992**, pp. 1495.
- 12 A. Streitwieser, J. X. Ni, *Tetrahedron Lett.* **1985**, 26, 6317–6320.
- 13 F. G. Bordwell, W. J. Bolye, K. C. Yee, *J. Am. Chem. Soc.* **1970**, 92, 5962–5932.
- 14 H. Hattori, *Appl. Catal. A* **2001**, 222, 247–259.
- 15 T. Seki, H. Kabashima, K. Akutsu, H. Tachikawa, H. Hattori, *J. Catal.* **2001**, 204, 393–401.
- 16 N. E. Fouad, P. Thomasson, H. Knözinger, *Appl. Catal. A* **2000**, 194/195, 213–225.
- 17 G. Suzukamo, M. Fukao, M. Minobe, *Chem. Lett.* **1987**, 585–588.
- 18 H. Gorzawski, W. F. Hölderich, *J. Mol. Catal. A* **1999**, 144, 181–187.
- 19 T. Yamaguchi, J.-H. Zhu, Y. Wang, M. Komatsu, M. Ookawa, *Chem. Lett.* **1997**, 989–990.
- 20 Y. Ono, T. Baba, *Catal. Today* **1997**, 38, 321–337.
- 21 T. Baba, H. Handa, Y. Ono, *J. Chem. Soc. Faraday Trans.* **1994**, 90, 187–191.
- 22 J. Kijenski, P. Radomski, E. Fedorynska, *J. Catal.* **2001**, 203, 407–425.
- 23 S. Kaskel, K. Schlichte, *J. Catal.* **2001**, 201, 270–274.
- 24 D. Farrusseng, K. Schlichte, B. Spliethoff, A. Wingen, S. Kaskel, J. S. Bradley, F. Schüth, *Angew. Chem., Int. Ed.* **2001**, 40, 4204–4207.
- 25 S. Kaskel, D. Farrusseng, K. Schlichte, *Chem. Commun.* **2000**, 2481–2482.
- 26 S. Kaskel, K. Schlichte, B. Zibrowius, *Phys. Chem. Chem. Phys.* **2002**, 4, 1675–1681.
- 27 P. Llewellyn, S. Kaskel in *Handbook of Porous Solids*, Vol. 3 (F. Schüth,

References and Notes to Section 1.2.2

- 1 J. Weitkamp, M. Hunger, U. Rymsa, *Microporous Mesoporous Mater.* **2001**, 48, 255–270.
- 2 R. A. Sheldon, R. S. Downing, *Appl. Catal. A* **1999**, 189, 163–183.
- 3 W. F. Hölderich, *Catal. Today* **2000**, 62, 115–130.
- 4 K. Tanabe, *Solid Acids and Bases*, Academic Press, Ed., New York, **1970**, pp. 175.

- K. S. W. Sing and J. Weitkamp, (Eds.), Wiley-VCH, Weinheim, **2002**, p. 2063–2086.
- 28 L. R. M. Martens, P. J. Grobet, P. A. Jacobs, *Nature* **1985**, 315, 568–570.
 - 29 L. R. M. Martens, W. J. M. Vermeiren, P. J. Grobet, P. A. Jacobs, *Stud. Surf. Sci. Catal.* **1987**, 31, 531–542.
 - 30 P. J. Grobet, L. R. M. Martens, W. J. M. Vermeiren, D. R. C. Huybrechts, P. A. Jacobs, *Z. Phys. D* **1989**, 12, 37–40.
 - 31 E. J. Doskocil, R. J. Davis, *J. Catal.* **1999**, 188, 353–364.
 - 32 M. G. Stevens, H. C. Foley, *Chem. Commun.* **1997**, 519–520.
 - 33 M. G. Stevens, M. R. Anderson, H. C. Foley, *Chem. Commun.* **1999**, 413–414.
 - 34 K. Tanabe, W. F. Hölderich, *Appl. Catal. A* **1999**, 181, 399–434.
 - 35 A. Mitsutani, *Catal. Today* **2002**, 73, 57–63.
 - 36 R. Rienäcker, J. Graefe, *Angew. Chem.* **1985**, 97, 348–349.
 - 37 H. Hattori, *Stud. Surf. Sci. Catal.* **1993**, 78, 35–49.
 - 38 H. Handa, T. Baba, H. Yamada, T. Takahashi, Y. Ono, *Catal. Lett.* **1997**, 44, 119–121.
 - 39 H. Matsushashi, H. Hattori, K. Tanabe, *Chem. Lett.* **1981**, 341–342.
 - 40 T. Baba, H. Yuasa, H. Handa, Y. Ono, *Catal. Lett.* **1998**, 50, 83–85.
 - 8 P. Knochel, A. Boudier, L. O. Bromm, E. Hupe, K. Knapp, J. A. Varela, H. Laaziri, F. Lhermitte, *Organoboranes for Synthesis*, B.C.S. Symposium Series 783, Chapter 3, Rds.: P. V. Ramachandran, H. C. Brown, Washington, D. C., 2001, 33.
 - 9 H. Laaziri, L. O. Bromm, F. Lhermitte, R. H. Gschwind, P. Knochel, *J. Am. Chem. Soc.* **1999**, 121, 6940.
 - 10 J. A. Varela, D. Peña, B. Goldfuss, K. Polborn, P. Knochel, *Org. Lett.* **2001**, 3, 2395.
 - 11 H. C. Brown, A. W. Moerikofer, *J. Am. Chem. Soc.* **1961**, 83, 3417.
 - 12 B. Goldfuss, P. Knochel, L. O. Bromm, K. Knapp, *Angew. Chem. Int. Ed.* **2000**, 39, 4136.
 - 13 L. O. Bromm, H. Laaziri, F. Lhermitte, K. Harms, P. Knochel, *J. Am. Chem. Soc.* **2000**, 122, 10218.

References and Notes to Section 1.2.3.2

References and Notes to Section 1.2.3.1

- 1 (a) H. C. Brown, B. C. Subba Rao, *J. Am. Chem. Soc.*, **1959**, 81, 6434; (b) H. C. Brown, G. Zweifel, *J. Am. Chem. Soc.*, **1966**, 88, 1433.
- 2 H. C. Brown, K. J. Murray, G. Müller, G. Zweifel, *J. Am. Chem. Soc.*, **1966**, 88, 1443.
- 3 R. Köster, W. Larbig, G. Rotermund, *Liebigs Ann. Chem.* **1965**, 682, 21.
- 4 S. E. Wood, B. Rickborn, *J. Org. Chem.* **1983**, 48, 555.
- 5 L. D. Field, S. P. Gallagher, *Tetrahedron Lett.* **1985**, 26, 6125.
- 6 F. Lhermitte, P. Knochel, *Angew. Chem. Int. Ed.* **1998**, 37, 2459.
- 7 E. Hupe, D. Denisenko, P. Knochel, *Tetrahedron* **2003**, 59, 9187.
- 1 M. Larhed, A. Hallberg, chapter IV.2.1.1.B.vii in E. Negishi, *Handbook of Organopalladium Chemistry for Organic Synthesis*, Vol. I, pp. 1143–1147, Wiley Interscience, **2002**.
- 2 R. C. Larock, W.-Y. Leung, S. Stolz-Dunn, *Tetrahedron Lett.* **1989**, 30, 6629–6632.
- 3 Examples: (a) L. F. Tietze, K. Kahle, T. Raschke, *Chem. Eur. J.* **2002**, 8, 401–407; (b) G. Dyker, H. Markwitz, G. Henkel, *Eur. J. Org. Chem.* **2001**, 2415–2423; (c) G. Dyker, D. Kadzimirsz, *Eur. J. Org. Chem.* **2003**, 3167–3172.
- 4 macrocycles: (a) G. Dyker, P. Grundt, *Eur. J. Org. Chem.* **1999**, 323–327; (b) G. Dyker, D. Kadzimirsz, G. Henkel, *Tetrahedron Lett.* **2003**, 44, 7905–7907.
- 5 G. Dyker, A. Thöne, *J. Prakt. Chem./Chemiker-Ztg.* **1999**, 341, 138–141.
- 6 Unpublished results; related publications: (a) G. Dyker, P. Grundt, *Tetrahedron Lett.* **1996**, 37, 619–622; (b) G. Dyker, P. Grundt, H. Markwitz, G. Henkel, *J. Org. Chem.* **1998**, 63, 6043–6047; (c) G. Dyker, P. Grundt, *Helv. Chim. Acta* **1999**, 82, 588–596.
- 7 R. C. Larock, M.-Y. Kuo, *Tetrahedron Lett.* **1991**, 32, 569–573.

- 8 G. Dyker, H. Markwitz, *Synthesis* **1998**, 1750–1754.

References and Notes to Section 1.2.3.3

- 1 S. Otsuka, K. Tani, Asymmetric Catalytic Isomerization of Functionalized Olefins, In *Asymmetric Synthesis*, Vol. 5, Chiral Catalysis, J. D. Morrison, Ed.; Academic Press: Orlando, 1985, pp. 171–191.
- 2 S. Otsuka, K. Tani, Isomerization of Olefin and the Related Reactions, In *Transition Metals for Organic Synthesis*, M. Beller, C. Bolm, Eds.; Wiley-VCH: Weinheim, Vol. 1, 2004, pp. 199–2009.
- 3 S. Akutagawa, K. Tani, Asymmetric isomerization of allylamines, In *Catalytic Asymmetric Synthesis*, 2. Ed., I. Ojima, Ed.; Wiley-VCH: New York, 2000, pp. 145–161.
- 4 S. Akutagawa, Isomerization of Carbon–Carbon Double Bonds, In *Comprehensive Asymmetric Catalysis*, E. N. Jacobsen, A. Pfaltz, S. Yamamoto, Eds.; Part II, Springer: Berlin, 1999, p. 813–830.
- 5 V. A. Soloshonok, A. G. Kirilenko, S. V. Galushko, V. P. Kukhar, *Tetrahedron Lett.* **1994**, 35, 5063–5064. D. Liu, S. A. Kozmin, *Angew. Chem. Int. Ed.* **2001**, 40, 4757–4759.
- 6 Z. Chen, R. Halterman, *J. Am. Chem. Soc.* **1992**, 114, 2267–2277.
- 7 K. Tani, T. Yamagata, S. Akutagawa, H. Kumobayashi, T. Taketomi, H. Takaya, A. Miyashita, R. Noyori, S. Otsuka, *J. Am. Chem. Soc.* **1984**, 106, 5208–5217.
- 8 S. Otsuka, K. Tani, *Synthesis* **1991**, 665. S.-I. Inoue, H. Takaya, K. Tani, S. Otsuka, T. Saito, R. Noyori, *J. Am. Chem. Soc.* **1990**, 112, 4897–4905.
- 9 Ref. 4, p. 826–827.
- 10 K. Tani, *Pure Appl. Chem.* **1985**, 57, 1845.
- 11 K. Tanaka, S. Qiao, M. Tobisu, M. M.-C. Lo, G. C. Fu, *J. Am. Chem. Soc.* **2000**, 122, 9870–9870. K. Tanaka, G. C. Fu, *J. Org. Chem.* **2001**, 66, 8177–8186.
- 12 K. Hiroya, K. Kurihara, K. Ogasawara, *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 2287.
- 13 M. Kitamura, K. Manabe, R. Noyori, H. Takaya, *Tetrahedron Lett.* **1987**, 28, 4719–4720.
- 14 M. Suzuki, A. Yanagisawa, R. Noyori, *J. Am. Chem. Soc.* **1985**, 107, 3348–3349.
- 15 K. Hiroya, K. Ogasawara, *J. Chem. Soc., Chem. Commun.* **1995**, 2205–2206.
- 16 H. Frauenrath, D. Brethauer, S. Reim, M. Maurer, G. Raabe, *Angew. Chem. Int. Ed.* **2001**, 40, 177–179.
- 17 H. Frauenrath, S. Reim, A. Wiesner, *Tetrahedron: Asymmetry* **1998**, 9, 1103.
- 18 H. Frauenrath, M. Kaulard, *Synlett* **1994**, 517.

References to Section 1.2.3.4

- 1 T. Junk, W. J. Catallo, *Chem. Soc. Rev.* **1997**, 26, 401; N. Elander, J. R. Jones, S.-Y. Lu, S. Stone-Elander, *Chem. Soc. Rev.* **2000**, 29, 239.
- 2 M. Yamamoto, K. Oshima, S. Matsubara, *Chem. Lett.* **2004**, 33, 846; J. Yao, R. F. Evilia, *J. Am. Chem. Soc.* **1994**, 116, 11229; T. Junk, W. J. Catallo, *Tetrahedron Lett.* **1996**, 37, 3445; K. Fodor-Csorba, G. Galli, S. Holly, E. Gács-Baitz, *Tetrahedron Lett.* **2002**, 43, 3789;
- 3 N. H. Werstiuk, T. Kadai, *Can. J. Chem.* **1985**, 63, 530; N. H. Werstiuk, T. Kadai, *Can. J. Chem.* **1974**, 52, 2169.
- 4 A. L. Anet, M. St. Jacques, *J. Am. Chem. Soc.* **1966**, 88, 2585.
- 5 J. L. Ganet, R. J. Hodges, *J. Am. Chem. Soc.* **1967**, 89, 4546; J. L. Ganet, J. C. West, *Aust. J. Chem.* **1974**, 27, 129.
- 6 N. F. Goldshleger, M. B. Tyabin, A. E. Shilov, A. A. Shteinman, *Zh. Fiz. Khim.* **1969**, 43, 2174; A. E. Shilov, A. A. Steinman, *Coord. Chem. Rev.* **1977**, 24, 97.
- 7 (a) Rh: C. P. Lenges, P. S. White, M. Brookhart, *J. Am. Chem. Soc.* **1999**, 121, 4385; (b) Co: T. A. Weil, S. Friedman, I. Wender, *J. Org. Chem.* **1974**, 39, 48; C. P. Lenges, M. Brookhart, B. E. Grant, *J. Organometal. Chem.* **1997**, 528, 199; (c) Ru: M. Ogasawara, M. Saburi, *Organometallics*, **1994**, 13, 1911; (d) Mn: C. Perthuisot, M. Fan,

- W. D. Jones, *Organometallics*, **1992**, 11, 3622; (e) Mo: C. Balzarek, D. R. Tyler, *Angew. Chem. Int. Ed. Engl.* **1999**, 38, 2406; (f) Pt: J. M. Barthez, A. V. Filikov, L. B. Frederiksen, M.-L. Huguet, J. R. Jones, S.-Y. Lu, *Can. J. Chem.* **1998**, 76, 726.
- 8 (a) R. Klei, J. T. Golden, T. D. Tilley, R. G. Bergman, *J. Am. Chem. Soc.* **2002**, 124, 2092; (b) L. P. Kingston, W. J. S. Lockley, A. N. Mather, E. Spink, S. P. Thompson, D. J. Wilkinson, *Tetrahedron Lett.* **2000**, 41, 2705; (c) G. J. Ellames, J. S. Gibson, J. M. Herbert, W. J. Kerr, A. H. McNeill, *Tetrahedron, Lett.* **2001**, 42, 6413.
 - 9 K. Ofosu-Asante, L. M. Stock, *J. Org. Chem.* **1986**, 51, 5452.
 - 10 J. D. Tanzer, B. Crist, Jr., *Macromolecules*, **1985**, 18, 1291.
 - 11 (a) H. Sajiki, K. Hattori, F. Aoki, K. Yasunaga, K. Hotta, *Synlett*, **2002**, 1149; (b) H. Sajiki, F. Aoki, H. Esaki, T. Maegawa, K. Horita, *Org. Lett.* **2004**, 6, 1485.
 - 12 D. Bröll, C. Kaul, A. Krämer, P. Krammer, T. Richter, M. Jung, H. Vogel, P. Zehner, *Angew. Chem. Int. Ed. Engl.*, **1999**, 38, 2998.
 - 13 N. Akiya and P. E. Savage, *Chem. Rev.*, **2002**, 102, 2725; P. E. Savage, *Chem. Rev.*, **1999**, 99, 603.
 - 14 A. R. Katritzky, S. M. Allin, and M. Siskin, *Acc. Chem. Res.*, **1996**, 29, 399.
 - 15 P. E. M. Siegbahn, M. R. A. Blomberg, and M. Svensson, *J. Phys. Chem.*, **1993**, 97, 2564.
 - 16 S. Matsubara, Y. Yokota, K. Oshima, *Chem. Lett.* **2004**, 33, 294.
 - 17 (a) Maier, W. F.; Roth, W.; Thies, I.; Schleyer, P. R. *Chem. Ber.* **1982**, 115, 808; (b) Takemura, Y.; Nakamura, A.; Taguchi, H.; Ouchi, K. *Ind. Eng. Chem. Prod. Res. Dev.* **1985**, 24, 213; (c) Tsuji, J.; Ohno, K. *J. Am. Chem. Soc.* **1968**, 90, 94; (d) Chatani, N.; Tatamidani, H.; Ie, Y.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2001**, 123, 4849.
 - 18 S. Matsubara, Y. Yokota, K. Oshima, *Org. Lett.* **2004**, 6, 2071.
 - 19 Oxidation of alcohol by hydrogen transfer in water under microwave irradiation: Takahashi, M.; Oshima, K.; Matsubara, S. *Tetrahedron Lett.* **2003**, 44, 9201.
 - 20 T. Kurihara, N. Ooba, S. Toyoda, and T. Maruno, *Oyobuturi*, **2002**, 71, 1508; T. Kaino, K. Jinguji, and S. Nara, *Appl. Phys. Lett.*, **1983**, 42, 567.
 - 21 A. Koshino and T. Tagawa, *J. Appl. Polym. Chem. Sc.* **1965**, 9, 117; M. S. Miller and I. M. Klotz, *J. Am. Chem. Soc.*, **1973**, 95, 5694.
 - 22 J. D. Tanzer and B. Crist, Jr. *Macromolecules*, **1985**, 18, 1291; L. C. Case and J. D. Atlas, *J. Polym. Sci.*, **1960**, 45, 435.
 - 23 M. Yamamoto, Y. Yokota, K. Oshima, and S. Matsubara, *Chem. Commun.* **2004**, 1714.

References and Notes to Section 1.2.4

- 1 (a) J. Tsuji, *Organic Synthesis with Palladium Compounds*, Springer, Heidelberg **1980**; (b) R. F. Heck, *Palladium Reagents in Organic Synthesis*, Academic Press, New York **1985**; (c) B. M. Trost, R. Verhoeven in *Comprehensive Organometallic Chemistry*, (Ed.: G. Wilkinson), Pergamon, Oxford, **1982**, 8, 799–838.
- 2 L. M. Stephenson, M. J. Grdina, M. Orfanopoulos, *Acc. Chem. Res.* **1980**, 13, 419–425.
- 3 (a) M. A. Umbreit, K. B. Sharpless, *J. Am. Chem. Soc.* **1977**, 99, 5526–5528; (b) L. M. Stevenson, D. R. Speth, *J. Org. Chem.* **1979**, 44, 4683–4689; (c) K. B. Sharpless, R. F. Lauer, *J. Am. Chem. Soc.* **1972**, 94, 7154–7155; (d) K. B. Sharpless, R. F. Lauer, *J. Org. Chem.* **1974**, 39, 429–430; (e) H. J. Reich, *J. Org. Chem.* **1974**, 39, 428–429; (f) H. J. Reich, S. Wollowitz, J. E. Trend, F. Chow, D. F. Wendelborn, *J. Org. Chem.* **1978**, 43, 1697–1705; (g) T. Hori, K. B. Sharpless, *J. Org. Chem.* **1978**, 43, 1689–1697.
- 4 J. Muzart, *Bull. Soc. Chim. Fr.* **1986**, 65–77.
- 5 J. L. Paih, G. Schlingloff, C. Bolm, in *Transition Metals for Organic Synthesis 2nd ed.* (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **2004**, 256–265; (b) M. B. Andrus, J. C. Lashley, *Tetrahedron* **2002**, 58, 845–866; (c) J. Eames, M. Watkinson, *Angew. Chem.* **2001**, 113,

- 3679–3683; *Angew. Chem. Int. Ed.* **2001**, 40, 3567–3571; (d) T. Katsuki, *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer Verlag Berlin Heidelberg, **1999**, Vol. 2, 791–799; (e) D. J. Rawlinson, G. Kharasch, *Synthesis* **1972**, 1–28.
- 6 H. Grennberg, J. E. Bäckvall, in *Transition Metals for Organic Synthesis 2nd ed.* (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **2004**, 243–255.
- 7 (a) M. S. Kharasch, G. Sosnovski, N. C. Yang, *J. Am. Chem. Soc.* **1959**, 81, 5819–5821; (b) M. S. Kharasch, G. Sosnovski, *J. Am. Chem. Soc.* **1958**, 80, 756; (c) M. S. Kharasch, S. Fono, *J. Org. Chem.* **1958**, 23, 324.
- 8 (a) C. Walling, A. A. Zavitsas, *J. Am. Chem. Soc.* **1963**, 85, 2084–2090; (b) J. K. Kochi, *J. Am. Chem. Soc.* **1962**, 84, 774–784.
- 9 A. L. J. Beckwith, A. A. Zavitsas, *J. Am. Chem. Soc.* **1986**, 108, 8230–8234.
- 10 H. Kropf, R. Schröder, R. Fölsing, *Synthesis* **1977**, 894–897.
- 11 G. Sosnovski, N. C. Yang, *J. Org. Chem.* **1960**, 25, 899–903. See also Ref. [2].
- 12 G. Sekar, A. Datagupta, V. K. Singh, *Tetrahedron Lett.* **1996**, 37, 8435–8436.
- 13 J. L. Bras, J. Muzart, *J. Mol. Catal. A: Chemical* **2002**, 185, 113–117.
- 14 F. Fache, O. Piva, *Synlett* **2002**, 2035–2036.
- 15 J. L. Bras, J. Muzart, *Tetrahedron Lett.* **2002**, 43, 431–433; (b) For the asymmetric variant see, J. L. Bras, J. Muzart, *Tetrahedron: Asymmetry* **2003**, 14, 1911–1915.
- 16 S. Carloni, B. Frullanti, R. Maggi, A. Mazzancani, F. Bigi, G. Sartori, *Tetrahedron Lett.* **2000**, 41, 8947–8950.
- 17 D. B. Denney, R. Napier, A. Cammarata, *J. Org. Chem.* **1965**, 30, 3151–3153.
- 18 M. Araki, T. Nagase, *Ger. Offen.* 26 25 030, **1976**; *Chem. Abstr.* **1977**, 86, 120886r.
- 19 (a) J. Muzart, *J. Mol. Cat.* **1991**, 64, 381–384; (b) A. Levina, J. Muzart, *Synth. Commun.* **1995**, 25, 1789–1794; (c) A. Levina, F. Hénin, J. Muzart, *J. Organomet. Chem.* **1995**, 494, 165–168; (d) A. Levina, J. Muzart, *Tetrahedron: Asymmetry* **1995**, 6, 147–156.
- 20 (a) M. T. Rispen, C. Zondervan, B. L. Feringa, *Tetrahedron: Asymmetry* **1995**, 6, 661–664; (b) C. Zondervan, B. L. Feringa, *Tetrahedron: Asymmetry* **1996**, 7, 1895–1898.
- 21 M. J. Södergren, P. G. Andersson, *Tetrahedron Lett.* **1996**, 37, 7577–7580.
- 22 A. S. Gokhale, A. B. E. Minidis, A. Pfaltz, *Tetrahedron Lett.* **1995**, 36, 1831–1834.
- 23 (a) M. B. Andrus, A. B. Argade, M. G. Pamment, *Tetrahedron Lett.* **1995**, 36, 2945–2948; (b) J. S. Clark, K. F. Tolhurst, M. Taylor, S. Swallow, *J. Chem. Soc., Perkin Trans. 1* **1998**, 1167–1169; (c) For the application of this catalyst to enantioselective alkyne oxidation, see J. S. Clark, K. F. Tolhurst, M. Taylor, S. Swallow, *Tetrahedron Lett.* **1998**, 39, 4913–4916.
- 24 (a) M. B. Andrus, X. Chen, *Tetrahedron* **1997**, 53, 16229–16240; (b) M. B. Andrus, Z. Zhou, *J. Am. Chem. Soc.* **2002**, 124, 8806–8807.
- 25 M. B. Andrus, D. Asgari, *Tetrahedron* **2000**, 56, 5775–5780.
- 26 G. Sekar, A. Datta Gupta, V. K. Singh, *J. Org. Chem.* **1998**, 63, 2961–2967.
- 27 M. B. Andrus, B. B. V. Soma Sekhar, *J. Heterocycl. Chem.* **2001**, 1265–1271.
- 28 (a) K. Kawasaki, S. Tsumura, T. Katsuki, *Synlett* **1995**, 1245–1246; (b) K. Kawasaki, T. Katsuki, *Tetrahedron* **1997**, 53, 6337–6350; (b) Y. Kohmura, T. Katsuki, *Tetrahedron Lett.* **2000**, 41, 3941–3945; (c) Y. Kohmura, T. Katsuki, *Synlett* **1999**, 1231–1234.
- 29 T.-H. Chuang, J.-M. Fang, C. Bolm, *Synth. Commun.* **2000**, 30, 1627–1641.
- 30 (a) A. V. Malkov, I. R. Baxendale, M. Bella, V. Langer, J. Fawcett, D. R. Russel, D. J. Mansfield, M. Valko, P. Kocovsky, *Organometallics* **2001**, 20, 673–690; (b) A. V. Malkov, M. Bella, V. Langer, P. Kocovsky, *Org. Lett.* **2000**, 2, 3047–3049.
- 31 G. Chelucci, G. Loriga, G. Murineddu, G. A. Pinna, *Tetrahedron Lett.* **2002**, 43, 3601–3604.
- 32 W.-S. Lee, H.-L. Kwong, H.-L. Chan, W.-W. Choi, L.-Y. Ng, *Tetrahedron: Asymmetry* **2001**, 12, 1007–1013.
- 33 (a) C. Bolm, J.-C. Frison, J. L. Paih, C. Moessner, *Tetrahedron Lett.* **2004**, 45,

- 5019–5021; (b) C. Bolm, J.-C. Frison, J. L. Paih, C. Moessner, G. Raabe, *J. Organomet. Chem.* **2004**, 689, 3767–3777.
- 34 (a) B. M. Trost, P. M. Metzner, *J. Am. Chem. Soc.* **1980**, 102, 3572–3577; (b) J. E. Bäckvall, K. Zetterberg, B. Åkermark, in *Inorganic Reactions and Methods* (Ed.: A. P. Hagen), VCH, **1991**, 12A, 123.
- 35 (a) P. M. Henry, G. A. Ward, *J. Am. Chem. Soc.* **1971**, 93, 1494–1497; (b) S. Wolfe, P. G. C. Campbell, *J. Am. Chem. Soc.* **1971**, 93, 1497–1499; (c) S. Wolfe, P. G. C. Campbell, *J. Am. Chem. Soc.* **1971**, 93, 1499–1501; (d) E. N. Frankel, W. K. Rohwedder, W. E. Neff, D. Weisleder, *J. Org. Chem.* **1975**, 40, 3247–3253.
- 36 (a) A. Heumann, B. Åkermark, *Angew. Chem. Int. Ed. Engl.* **1984**, 23, 453–454; (b) A. Heumann, B. Åkermark, S. Hansson, T. Rein, *Org. Synth.* **1990**, 68, 109–115; (c) S. Hansson, A. Heumann, T. Rein, B. Åkermark, *J. Org. Chem.* **1990**, 55, 975–984; (d) J. E. Bäckvall, R. E. Nordberg, E. Björkman, C. Moberg, *J. Chem. Soc., Chem. Commun.* **1980**, 943–944.
- 37 (a) B. Åkermark, E. M. Larsson, J. D. Oslob, *J. Org. Chem.* **1994**, 59, 5729–5733; (b) C. Jia, P. Müller, H. Mimoun, *J. Mol. Cat. A* **1995**, 101, 127–136.
- 38 (a) J. E. Bäckvall, R. B. Hopkins, H. Grennberg, M. M. Mader, A. K. Awasthi, *J. Am. Chem. Soc.* **1990**, 112, 5160–5166; (b) J. Wöltiger, J. E. Bäckvall, A. Zsigmond, *Chem. Eur. J.* **1999**, 5, 1460–1467; (c) S. E. Byström, E. M. Larsson, B. Åkermark, *J. Org. Chem.* **1990**, 55, 5674–5675.
- 39 (a) A. K. El-Quisiari, H. A. Quaseer, P. M. Henry, *Tetrahedron Lett.* **2002**, 43, 4229–4231; (b) R. C. Larock, T. R. Hightower, *J. Org. Chem.* **1993**, 58, 5298–5300; (c) M. Rönn, J. E. Bäckvall, P. G. Andersson, *Tetrahedron Lett.* **1995**, 36, 7749–7759; (d) M. Rönn, P. G. Andersson, J. E. Bäckvall, *Acta Chem. Scand.* **1997**, 51, 773–777.
- 40 (a) H. Grennberg, K. Bergstad, J. E. Bäckvall, *J. Mol. Cat. A* **1996**, 113, 355–358; (b) K. Bergstad, H. Grennberg, J. E. Bäckvall, *Organometallics* **1998**, 17, 45–50.
- 41 M. S. Chen, M. C. White, *J. Am. Chem. Soc.* **2004**, 126, 1346–1347.
- 42 J. E. Bäckvall, S. E. Byström, R. E. Nordberg, *J. Org. Chem.* **1984**, 49, 4619–4631.
- 43 A. Thorarensen, A. Palmgren, K. Itami, J. E. Bäckvall, *Tetrahedron Lett.* **1997**, 38, 8541–8544.
- 44 J. E. Bäckvall, J. E. Nyström, R. E. Nordberg, *J. Am. Chem. Soc.* **1985**, 107, 3676–3686.

References and Notes to Section 1.2.5

- 1 B. M. Trost, *Science* **1991**, 254, 1471.
- 2 I. Ojima, *Catalytic Asymmetric Synthesis*, 2nd ed., Wiley-VCH, New York, **2000**.
- 3 B. M. Trost, M. J. Krische, *Synlett* **1998**, 1.
- 4 C. Aubert, O. Buisine, M. Malacria, *Chem. Rev.* **2002**, 102, 813.
- 5 B. M. Trost, *Acc. Chem. Res.* **1990**, 23, 34.
- 6 H. M. R. Hofmann, *Angew. Chem. Int. Ed.* **1969**, 8, 557.
- 7 G. C. Lloyd-Jones, *Org. Biomol. Chem.* **2003**, 1, 215.
- 8 B. M. Trost, F. D. Toste, A. B. Pinkerton, *Chem. Rev.* **2001**, 101, 2067.
- 9 B. M. Trost, *Chem.-Eur. J.* **1998**, 4, 2405.
- 10 I. Ojima, M. Tzamaroudaki, Z. Li, R. J. Donovan, *Chem. Rev.* **1996**, 102, 813.
- 11 S. Yamazaki, K. Yamada, T. Otsubo, M. Haruna, E. Kutsuwa, H. Tamura, *Chem. Comm.* **2001**, 69.
- 12 B. M. Trost, M. Lautens, *J. Am. Chem. Soc.* **1985**, 107, 1781.
- 13 B. M. Trost, M. Lautens, C. Chan, D. J. Jebaratnam, T. Mueller, *J. Am. Chem. Soc.* **1991**, 113, 636.
- 14 B. M. Trost, G. J. Tanoury, *J. Am. Chem. Soc.* **1987**, 109, 4753.
- 15 M. Mori, in *Topics in Organometallic Chemistry*, Vol. 1 (Ed.: A. Furstner), Springer, Berlin, **1998**, p. 133.
- 16 B. M. Trost, D. C. Lee, F. Rise, *Tetrahedron Lett.* **1989**, 30, 651.
- 17 A. Goeke, M. Sawamura, R. Kuwano, Y. Ito, *Angew. Chem. Int. Ed.* **1996**, 35, 662.

- 18 M. Hatano, M. Terada, K. Mikami, *Angew. Chem. Int. Ed.* **2001**, 40, 249.
- 19 M. Hatano, K. Mikami, *J. Am. Chem. Soc.* **2003**, 125, 4704.
- 20 H. Ohno, K. Miyamura, Y. Takeoka, T. Tanaka, *Angew. Chem. Int. Ed.* **2003**, 42, 2647.
- 21 B. M. Trost, J. M. Tour, *J. Am. Chem. Soc.* **1987**, 109, 5268.
- 22 B. M. Trost, K. Matsuda, *J. Am. Chem. Soc.* **1988**, 110, 5233.
- 23 A. Ajamian, J. L. Gleason, *Org. Lett.* **2003**, 5, 2409.
- 24 J. L. Renaud, M. Petit, C. Aubert, M. Malacria, *Synlett* **1997**, 931.
- 25 S. J. Sturla, N. M. Kablaoui, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, 121, 1976.
- 26 N. Chatani, N. Furukawa, H. Sakurai, S. Murai, *Organometallics* **1996**, 15, 901.
- 27 A. Furstner, F. Stelzer, H. Szillat, *J. Am. Chem. Soc.* **2001**, 123, 11863.
- 28 M. Mendez, M. P. Munoz, C. Nevado, D. J. Cardenas, A. M. Echavarren, *J. Am. Chem. Soc.* **2001**, 123, 10511.
- 29 S. Oi, I. Tsukamoto, S. Miyano, Y. Inoue, *Organometallics* **2001**, 20, 3704.
- 30 B. M. Trost, A. Indolese, *J. Am. Chem. Soc.* **1993**, 115, 4361.
- 31 B. M. Trost, F. D. Toste, *J. Am. Chem. Soc.* **2000**, 122, 714.
- 32 B. M. Trost, F. D. Toste, *J. Am. Chem. Soc.* **1999**, 121, 9728.
- 33 M. Nishida, N. Adachi, K. Onozuka, H. Matsumura, M. Mori, *J. Org. Chem.* **1998**, 63, 9158.
- 34 J. L. Paih, D. Cuervo Rodriguez, S. Derien, P. H. Dixneuf, *Synlett* **2000**, 95.
- 35 R. Grigg, P. Stevenson, T. Worakun, *Tetrahedron* **1988**, 44, 4967.
- 36 P. Cao, B. Wang, X. M. Zhang, *J. Am. Chem. Soc.* **2000**, 122, 6490.
- 37 P. Cao, X. M. Zhang, *Angew. Chem. Int. Ed.* **2000**, 39, 4104.
- 38 A. W. Lei, M. S. He, S. L. Wu, X. M. Zhang, *Angew. Chem. Int. Ed.* **2002**, 41, 3457.
- 39 A. W. Lei, M. S. He, X. M. Zhang, *J. Am. Chem. Soc.* **2002**, 124, 8198.
- 40 A. W. Lei, J. P. Waldkirch, M. S. He, X. M. Zhang, *Angew. Chem. Int. Ed.* **2002**, 41, 4526.
- 41 A. W. Lei, M. S. He, X. M. Zhang, *J. Am. Chem. Soc.* **2003**, 125, 11472.
- 42 H. Chakrapani, C. Liu, R. A. Widenhoefer, *Organic Letters* **2003**, 5, 157.
- 43 K. M. Brummond, H. F. Chen, P. Sill, L. F. You, *J. Am. Chem. Soc.* **2002**, 124, 15186.
- 44 N. Chatani, H. Inoue, T. Morimoto, T. Muto, S. Murai, *J. Org. Chem.* **2001**, 66, 4433.
- 45 A. J. Fletcher, S. D. R. Christie, *J. Chem. Soc., Perkin Transactions I* **2000**, 1657.
- 46 J. Tsuji, *Transition Metal Reagents and Catalysts: Innovations in Organic Synthesis*, Wiley, Chichester, UK, **2000**.
- 47 G. Calvin, G. E. Coates, *J. Chem. Soc.* **1960**, 2008.
- 48 J. P. Collman, L. S. Hegeus, J. R. Norton, R. G. Finke, *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Valley, CA, **1987**.
- 49 M. Lautens, J. Mancuso, *Org. Lett.* **2000**, 2, 671.
- 50 B. M. Trost, C. Pedregal, *J. Am. Chem. Soc.* **1992**, 114, 7292.
- 51 S.-Y. Onozawa, Y. Hatanaka, N. Choi, K. Tanaka, *Organometallics* **1997**, 16, 5389.
- 52 B. M. Trost, F. D. Toste, *J. Am. Chem. Soc.* **2002**, 124, 5025.
- 53 J. Tsuji, *Palladium Reagents and Catalysts. Innovations in Organic Synthesis*, Wiley, New York, **1995**.
- 54 J. M. Takacs, F. Clement, J. Y. Zhu, S. V. Chandramouli, X. P. Gong, *J. Am. Chem. Soc.* **1997**, 119, 5804.
- 55 J. M. Takacs, Y. C. Myoung, *Tetrahedron Lett.* **1992**, 33, 317.
- 56 C. W. Holzhapfel, L. Marais, *Tetrahedron Lett.* **1998**, 39, 2179.
- 57 T. Doi, A. Yanagisawa, S. Nakanishi, K. Yamamoto, T. Takahashi, *J. Org. Chem.* **1996**, 61, 2602.
- 58 W. Oppolzer, D. L. Kuo, M. W. Hutzinger, *Tetrahedron Lett.* **1997**, 38, 6213.
- 59 X. F. Tong, Z. G. Zhang, X. M. Zhang, *J. Am. Chem. Soc.* **2003**, 125, 6370.
- 60 S. T. Diver, A. J. Giessert, *Chem. Rev.* **2004**, 104, 1317.
- 61 L. S. Hegeus, *Transition Metals in the Synthesis of Complex Organic Molecules*,

- 2nd ed., University Science Books, Sausalito, CA, 1999.
- 62 B. M. Trost, Y. Li, *J. Am. Chem. Soc.* **1996**, *118*, 6625.
 - 63 B. M. Trost, J. Dumas, M. Villa, *J. Am. Chem. Soc.* **1992**, *114*, 9836.
 - 64 I. Nakamura, Y. Yamamoto, *Chem. Rev.* **2004**, *104*, 2127.
 - 65 K. Harada, Y. Tono, H. Kato, Y. Fukuyama, *Tetrahedron Lett.* **2002**, *43*, 3829.
 - 66 B. M. Trost, J. R. Corte, M. S. Gudiksen, *Angew. Chem. Int. Ed.* **1999**, *38*, 3662.
 - 67 B. M. Trost, J. R. Corte, *Angew. Chem. Int. Ed.* **1999**, *38*, 3664.
 - 68 B. M. Trost, C. D. Haffner, D. J. Jebaratnam, M. J. Krische, A. P. Thomas, *J. Am. Chem. Soc.* **1999**, *121*, 6183.
 - 69 B. Trost, M. J. Krische, *J. Am. Chem. Soc.* **1999**, *121*, 6131.
 - 70 P. A. Jacobi, P. Herradura, *Tetrahedron Lett.* **1997**, *38*, 6621.
 - 71 M. He, Ph.D. thesis, Penn State University (University Park), **2004**.
 - 72 G. D. P. Barry M. Trost, and Andreas Schoop, *J. Am. Chem. Soc.* **1998**, *120*, 9228.
 - 73 J. Montgomery, *Acc. Chem. Res.* **2000**, *33*, 467.
 - 74 M. Mori, N. Uesaka, F. Saitoh, M. Shibasaki, *J. Org. Chem.* **1994**, *59*, 5643.

References and Notes to Section 1.3

- 1 G. Dyker, *Polycyclic Ring Systems via Palladacycles as Reactive Intermediates*, in: *Organic Synthesis via Organometallics OSM 5*, G. Helmchen (Ed.), pages 129–137, Vieweg **1997**.
- 2 G. Dyker, *Chem. Ber./Recueil* **1997**, *130*, 1567–1578.
- 3 G. Dyker, *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1023–1025.

- 4 R. Suau, J. M. Lopez-Romero, R. Rico, *Tetrahedron* **1997**, *42*, 14397–14410.
- 5 G. Dyker, *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 103–105.
- 6 G. Dyker, *J. Org. Chem.* **1993**, *58*, 6426–6428.
- 7 G. Dyker, *Chem. Ber.* **1994**, *127*, 739–742.
- 8 O. Baudoin, A. Herrbach, F. Gueritte, *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 5736–5740.

References and Notes to Section 1.4

- 1 Transition metal catalyzed C–H to C–C transformations: (a) F. Kakiuchi, N. Chatani, *Adv. Synth. Catal.* **2003**, *345*, 1077–1101; (b) V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev.* **2002**, *102*, 1731–1770; (c) Y. Guari, S. Sabo-Etienne, B. Chaudret, *Eur. J. Inorg. Chem.* **1999**, 1047–1055; (d) G. Dyker, *Angew. Chem. Int. Ed.* **1999**, *38*, 1698–1712.
- 2 Platinum catalyzed functionalization of amino acids: B. D. Dangel, J. A. Johnson, D. Sames, *J. Am. Chem. Soc.* **2001**, *123*, 8149–8150.
- 3 Ruthenium catalyzed C–C bond formation directed by pyridine: a) C.-H. Jun, D.-C. Hwang, S.-J. Na, *Chem. Commun.* **1998**, 1405–1406; b) N. Chatani, T. Asaumi, S. Yorimitsu, T. Ikeda, F. Kakiuchi, S. Murai, *J. Am. Chem. Soc.* **2001**, *123*, 10935–10941.
- 4 Arylation of a cyclopalladated complex derived from tri-(*o*-tolyl)-phosphine with phenylstannane: J. Louie, J. F. Hartwig, *Angew. Chem. Int. Ed.* **1996**, *35*, 2359–2361.
- 5 Coupling of a Schiff base cyclopalladated complex with boronic acids: B. D. Dangel, K. Godula, S. W. Youn, B. Sezen, *J. Am. Chem. Soc.* **2002**, *124*, 11856–11857.
- 6 B. Sezen, R. Franz, D. Sames, *J. Am. Chem. Soc.* **2002**, *124*, 13372–13373.

2

C–H Transformation at Unfunctionalized Alkanes

2.1

C–O Bond Formation by Oxidation

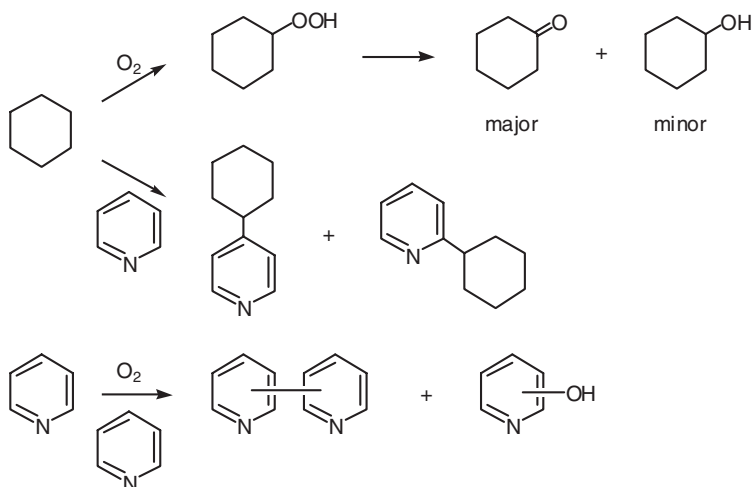
2.1.1

Gif Reactions

Pericles Stavropoulos, Remle Çelenligil-Çetin, Salma Kiani, Amy Tapper, Devender Pinnapareddy, and Patrina Paraskevopoulou

2.1.1.1 Introduction and Fundamental Examples

Gif chemistry [1] refers to the use of a host of iron and, to a lesser extent, copper-based reagents for oxygenation/ketonization of aliphatic hydrocarbons in pyridine/carboxylic acid solutions. Gif reactions and reagents were first introduced by Sir Derek Barton in 1983 and named after the birthplace of their invention (Gif-sur-Yvette, France) [2]. The development of Gif reagents is preceded by the early work of Tabushi and coworkers [3], who first reported the system $[\text{Fe}(\text{salen})]_2\text{O}/2$ -mercaptoethanol for oxygenation of adamantane in pyridine, with an unusual selectivity for oxygenation of secondary positions. Among the wide range of substrates targeted for Gif-type oxygenations, cycloalkanes have been historically regarded as the prime candidates [4], because of the inherent abundance of sec C–H sites and involvement of some of the compounds in the Nylon industry [5] (one/ol mixture derived from cyclohexane and cyclododecane). Scheme 1 details the classes of products obtained in oxygenations of cyclohexane under typical Gif conditions. Oxygenated end-products originate from the intermediate alkyl hydroperoxide initially formed as a result of the reaction of incipient alkyl radicals with dioxygen, and occasionally detected in low yields in the reaction profile [4]. Most of the alkyl hydroperoxide is converted to the corresponding ketone (major product) and alcohol (minor product) by Fe(II)-mediated decomposition of ROOH (largely leading to ketone) and/or reduction to alcohol in the presence of any added reducing agent (usually Zn, Fe, thiol, or phosphine). In addition to oxo products, and under low partial pressures of dioxygen, alkylpyridines are obtained by attack of alkyl radicals selectively at positions 2 and 4 of the protonated pyridine. Pyridine constitutes the sine qua non matrix of Gif chemistry, but is itself susceptible to oxidative attack, providing all possible bipyridines (with some selec-



Scheme 1. Major classes of products in Gif oxygenation chemistry

tivity toward reaction at positions 2 and 4) and hydroxypyridines, the latter being favored with increasing partial pressures of dioxygen.

Table 1 summarizes major branches of the Gif family of reagents as developed chronologically by Barton's group. Two types of reagent are evident: (1) those that employ dioxygen and a sacrificial reducing agent (Zn, Fe, thiols); and (2) those that make use of a reduced form of dioxygen (O_2^- , H_2O_2 , t -BuOOH). The most practical reagent in the former category is the heterogeneous Gif^{IV} system, involving $Fe_{cat}/O_2/Zn$ in pyridine/acetic acid (10:1 v/v). The iron catalyst is usually $[Fe_3O(OAc)_6(py)_3] \cdot 0.5py$, but other iron precursors are equally effective. The latter category is best represented by the homogeneous GoAgg^{III} system – $FeCl_3/PicH/H_2O_2$ ($PicH = 2$ -picolinic acid) in pyridine or pyridine/acetic acid (10:1 v/v). Two or more picolinic acid anions chelate with the metal and reportedly enhance the rate of the Gif reaction by fiftyfold over acetate as the sole source of carboxylic acid. The presence of a carboxylic acid in the solvent matrix is necessary, otherwise disproportionation of H_2O_2 is merely observed at the expense of substrate oxygenation [6]. Several Gif-type reagents (for instance, $[trans-Fe(O_2CCH_3)_2(py)_4]$, $[Fe_2(O_2CCH_3)_4(py)_3]_n$, $[Fe(Pic)_2(py)_2]$, $[Fe_2O(Pic)_4(py)_2]$, $[Fe(O_2CCF_3)_2(py)_4]$, $[Fe_2O(O_2CCF_3)_4(py)_6]$, $[Fe(O_2CCMe_3)_2(py)_4]$, and $[Fe_3O(O_2CCMe_3)_6(py)_3]^{0/+}$) were subsequently developed by our group [7], incorporating different carboxylic acids (AcOH, PicH, TFA, and PivH) in the coordination sphere of the metal center and in the fluid matrix. Acetic acid and pivalic acid stabilize $Fe(III)$ precursor species and sustain only O_2 /reductant-dependent systems, whereas picolinic acid and trifluoroacetic acid favor $Fe(II)$ -centered reagents supported by H_2O_2 . Use of both ferrous and ferric compounds with a range of carboxylic acids facilitated mechanistic re-evaluation of the two major classes of Gif reagents [1].

Table 1. Barton's Gif oxygenation systems.

System	Precatalyst	Oxidant	Reductant	Solvent ^c	Ref.
Gif ^I	None added ^a	O ₂	Fe ⁰ /Na ₂ S	py/AcOH (10:1 v/v)	8
Gif ^{II}	None added ^a	O ₂	Fe ⁰ /H ₂ S	py/AcOH/H ₂ O (6.6%)	8, 9
Gif ^{III}	None added ^a	O ₂	Fe ⁰	py/AcOH/H ₂ O (6.6%)	10
Gif ^{IV}	Fe ^{II/III} b	O ₂	Zn	py/AcOH/H ₂ O ^d (6.6%)	10
GO	Fe ^{II/III} b	O ₂	Hg cathode	py/CF ₃ COOH	11
GoAgg ^I	Fe ^{II}	KO ₂ ^c		py/AcOH	12
GoAgg ^{II}	Fe ^{III} f	H ₂ O ₂ (30%) ^g		py/AcOH	12, 13
GoAgg ^{III}	Fe ^{III} f/PicH (1:3)	H ₂ O ₂ (30%) ^g		py/AcOH (or py)	14
GoChAgg ^I	Cu ^{II}	H ₂ O ₂ (30%) ^g		py/AcOH (or py)	15
GoChAgg ^{II}	None added ^a	O ₂	Cu ⁰	py/AcOH	16
GoAgg ^{IVh}	Fe ^{III} i	<i>t</i> -BuOOH (90%) ^g		py/AcOH, 60 °C	17
GoAgg ^{Vh}	Fe ^{III} i/PicH (1:3)	<i>t</i> -BuOOH (90%) ^g		py/AcOH, 60 °C	17

^a Although no compound is added, the zero-valent metal partially dissolves in solution

^b Usually [Fe₃O(OAc)₆(py)₃].0.5py

^c At room temperature, unless otherwise noted

^d Addition of H₂O is optional

^e Under inert gas (Ar, N₂)

^f Usually FeCl₃·6H₂O

^g Under inert gas or O₂

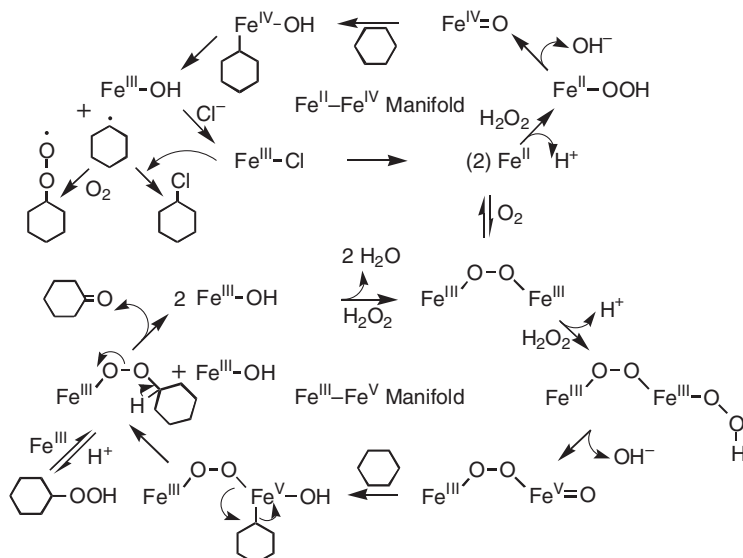
^h Later expelled from the Gif family [17]

ⁱ Usually Fe(NO₃)₃·9H₂O

2.1.1.2 Mechanism

Gif chemistry provoked a long-standing mechanistic controversy among proponents of nonradical pathways (largely championed by Barton and co-workers) and critics favoring the involvement of diffusively free radicals in Gif oxygenation reactions (heralded by prominent members of the physical–organic community). Barton's mechanism [18] underwent considerable modification with the accumulation of new evidence, culminating in an all-encompassing dual manifold scheme (Scheme 2, formulated for Gif/H₂O₂ systems) involving Fe(III)/H₂O₂ Gif chemistry responsible for a nonradical Fe(III)/Fe(V) cycle, and circumstantial Fe(II)/H₂O₂ interactions giving rise to a radical-bearing Fe(II)/Fe(IV) path [6]. The two manifolds reportedly interconnect by means of reversible dioxygen activation by Fe(II) sites leading to generation of diferric peroxo intermediates, the implication being that, under conditions of dioxygen deficiency, the nonradical Fe(III)/Fe(V) path may be diverted to the radical Fe(II)/Fe(IV) cycle. The active oxidants in both

manifolds are perceived to be high-valent iron–oxo units (Fe(V)=O and Fe(IV)=O , respectively), which are capable of activating C–H bonds in a $[2 + 2]$ addition manner. The side-on approach at the C–H bond-activating step was deemed to be consistent with the alleged selectivity of Gif chemistry toward secondary positions and the observed kinetic isotope effects ($\text{KIE} \approx 2$ for both manifolds) [2]. The two manifolds differentiate at the level of the resulting organometallic intermediates: the HO–Fe(V)–R unit was perceived to be stable enough to survive transformation to a metal-bound alkylperoxo intermediate, whereas the analogous HO–Fe(IV)–R unit was thought to be susceptible to homolytic cleavage, leading to carbon-centered radicals and products thereof. Exceptional cases of HO–Fe(V)–R instability associated with formation of alkyl radicals were also noted for bulky R groups, most prominently exemplified by the *tert*-adamantyl (but not *sec*-adamantyl) moiety [4]. Conspicuously absent in both manifolds was the possible involvement of oxygen-centered radicals (either hydroxyl radicals or substrate derived alkoxy radicals) in the C–H activation step.



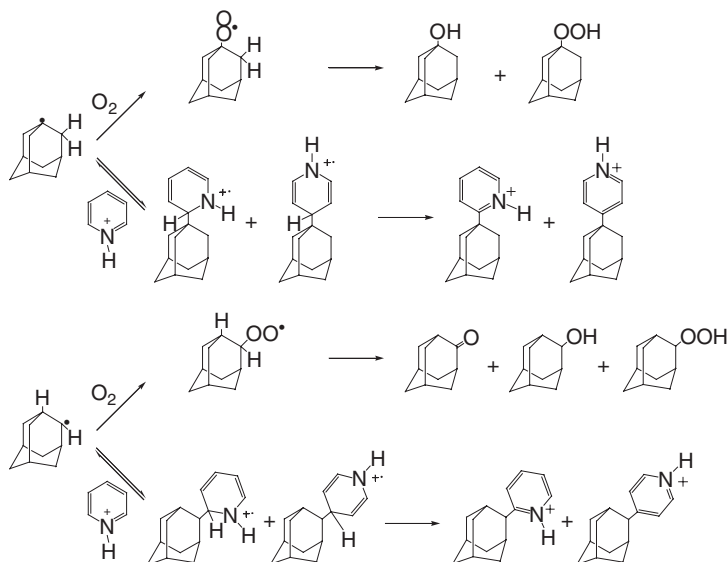
Scheme 2. Barton's dual manifold mechanism of Gif chemistry.

The applicability of the nonradical mechanism was first contested by Perkins [19] in an early publication reporting the oxygenation of cyclohexane by a GoAgg^{II} -type system that was shown to generate cyclohexyl radicals in spin-trapping experiments. Moreover, labeling studies indicated that the oxygen content of the resulting cyclohexylhydroperoxide was derived from dioxygen, thus suggesting a key role for the reaction of diffusively free alkyl radicals with dioxygen ($\text{R}^\bullet + \text{O}_2 \rightarrow \text{ROO}^\bullet$). The same system was also found to mediate para-hydroxylation of phenylalanine in a manner consistent with that expected for HO^\bullet radical involvement. These results were only qualitative in nature and did not receive due attention at the time. Nevertheless, the incorporation of dioxygen into the alkylhy-

droperoxide was a decisive finding that precipitated a revision of Barton's mechanism to account for dioxygen insertion into the metal-bound, rather than diffusively free, alkyl radical moiety [4]. A series of subsequent publications by Minisci [20] on Gif/*t*-BuOOH systems (GoAgg^{IV/V}) provided compelling evidence in support of a typical Haber–Weiss mechanism, involving H-atom abstraction from substrate C–H bonds by *t*-BuO•/*t*-BuOO• radicals with concomitant generation of diffusively free alkyl radicals. Other GoAgg^V systems supported by diagnostic organic hydroperoxides were studied by Ingold [21] and confirmed the preponderant role of radical chemistry with Gif/*t*-BuOOH systems. Eventually Barton concurred with these results and expelled this branch of reagents from the bona fide Gif family [17]. It is noteworthy that Minisci identified a major role for *t*-BuO•/*t*-BuOO• radicals even with *t*-BuOOH-supported metalloporphyrin reagents [22]. Although this work cast doubt on the totality of Gif chemistry, experimental evidence for the major Gif/H₂O₂ and Gif/O₂/Red systems had remained scarce, and included Perkins' work [19] noted above, and Newcomb's examination of ultrafast radical probes under GoAgg^{III} conditions [23], confirming the presence of diffusively free substrate radicals. The latter study was interpreted by Barton as an exceptional case of substrate–radical involvement, similar to that encountered with the tertiary position of adamantane [18]. Finally, an influential review by Perkins [24] summarized the findings in favor of a radical reinterpretation of Gif chemistry by providing a critical re-examination of Barton's experimental results and pinpointing fallacies and misinterpretations.

Our work [7] provided much needed experimental evidence enabling resolution of the mechanistic discrepancies surrounding the major Gif/H₂O₂ (GoAgg^{III}) and Gif/O₂/Zn (Gif^{IV}) systems. A two-step approach was implemented: (1) we first examined whether substrate-derived, carbon-centered radicals may be responsible for the typical product profiles of Gif chemistry; and (2) we then explored whether oxygen-centered radicals (in particular hydroxyl radicals) were the major H-atom abstracting agents in Gif solutions. Adamantane has been the substrate of choice because of its historic value in the development of Gif chemistry. As previously noted, Barton maintained that the *sec* C–H positions of adamantane were oxygenated via a nonradical mechanism, whereas the *tert* C–H sites were susceptible to radical oxygenation paths. A major observation contributing to this conclusion was the detection of *tert*- but not *sec*-adamantylpyridines in the product profile of Gif oxygenations [13]. However, in our hands, significant amounts of *sec*-adamantylpyridines were also obtained in oxygenations of adamantane by Gif-type Fe(II)/H₂O₂ and Fe(III)/H₂O₂ systems, especially under low partial pressures of dioxygen. To place these results in a quantitative context, we employed authentic *tert*- and *sec*-adamantyl radicals, generated by photolysis of the corresponding Barton PTOC esters [13], and studied the partitioning of these radicals between dioxygen and protonated pyridine in py/AcOH solutions under a stream of 4% O₂ in dinitrogen. To better mimic the conditions of the actual Gif experiment, catalytic amounts of Fe(II) or Fe(III) reagents were added to the reaction mixture, but no H₂O₂. Scheme 3 indicates the oxygen- and pyridine-trapped adamantyl products, which were quantified to afford Ad(O)/Ad-py ratios of 0.03 for the tertiary position

and 5.4 for the secondary position. These numbers reflect the fact that while both radicals are captured by dioxygen at diffusion-controlled rates, the *reversible* addition of the radicals to protonated pyridine reportedly [25] proceeds at significantly different rates for the two radicals ($k_{\text{obs}} = 2.2 \times 10^6$ and $1.3 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ for *tert*- and *sec*-adamantyl radicals, respectively). Most importantly, these ratios were comparable with the corresponding values furnished by the product profiles of Gif oxygenations of adamantane (both Fe(II)/H₂O₂ and Fe(III)/H₂O₂ systems) carried out under identical conditions. Bearing in mind Barton's contention about the diversion of the nonradical Fe(III)–Fe(V) cycle to the radical Fe(II)–Fe(IV) path under conditions of dioxygen deficiency, we sought to repeat the competitive experiments under 100 % dioxygen, by enabling TEMPO to compete with dioxygen for capturing *tert*/*sec*-adamantyl radicals. Once again, there was a close correspondence between ratios of Ad-TEMPO/Ad(O) (evaluated individually for *tert* and *sec* sites) provided by the use of authentic adamantyl radicals and the product profile of typical Gif oxygenations of adamantane. Taken together, these results provide compelling evidence for the central role of diffusively free carbon-centered radicals in determining the entire product profile of Gif chemistry.



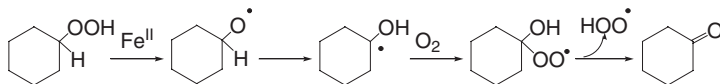
Scheme 3. Competition between dioxygen and pyridinium for trapping *tert*- and *sec*-adamantyl radicals.

We next examined the possibility that HO[•] radicals, rather than metal-bound oxidants, were the main H-atom abstraction agents in Gif solutions. This was suggested by *tert*/*sec* selectivity ratios for activation of C–H bonds of adamantane, which, under inert atmosphere, were as low as 2.2, progressively increasing with increasing partial pressures of dioxygen. The lower end value is consistent with known HO[•] radical kinetics, whereas increasing *tert*/*sec* values reflect the participation of a more selective H-atom-abstracting agent operating in tandem with

HO^\bullet radicals [26]. These results were also consistent with intramolecular kinetic isotope effect measurements on typical Gif oxygenations of 1,3- d_2 -adamantane to 1-adamantanol, which furnished a value of 1.06(6) under N_2 and 1.73(2) under 4% O_2 in N_2 . The former value is in agreement with what is expected for the action of HO^\bullet radicals in fluid media [24], whereas the latter value indicates again the intervention of an additional, more selective oxidant. The involvement of hydroxyl radicals was further confirmed by the characteristic addition of HO^\bullet radicals to DMSO (Eq. 1) in competition with H-atom abstraction from ethanol (Eq. 2) under Gif oxygenation conditions. The resulting carbon-centered radicals were trapped by the intrinsic solvent matrix ($\text{py}/[\text{pyNH}]^+$) and quantified as alkyl pyridines under inert atmosphere. The average $k_{\text{EtOH}}/k_{\text{DMSO}}$ value obtained (0.32(4)) and the selectivity for H-atom abstraction from the α - versus β -position of ethanol were both consistent with known HO^\bullet radical kinetics [27].



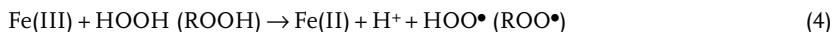
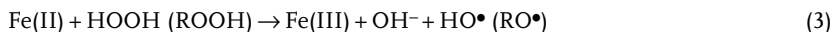
The second, more selective oxidant noted above is expected to be substrate-derived alkoxy radicals, generated via metal-dependent decomposition of the intermediate alkylhydroperoxide. Indeed, 1-AdOOH has been shown [1] to support Gif-type oxygenation of adamantane with *tert*/sec selectivity (~ 9) consistent with that expected for 1-AdO $^\bullet$ radicals. Most interestingly, 2-AdOOH was found *not* to support oxygenation of adamantane, but merely undergoes decomposition to afford largely 2-adamantanone and minor amounts of 2-adamantanol. The preponderance of ketones over sec alcohols is a general phenomenon in Gif chemistry and is suspected to be because of a pyridine-enabled 1,2-H atom migration step [28], competing effectively with, and at the expense of, the usual H-atom abstraction reaction of sec alkoxy radicals (Scheme 4).



Scheme 4. Generation of cyclohexanone from cyclohexylhydroperoxide via a 1,2-H atom shift mechanism.

The critical role of Fe(II) ions in the generation of active oxidants in Gif chemistry is well established not only for O_2 /Red-dependent systems but also for Gif reagents supported by H_2O_2 . Carboxylic acids such as acetic and pivalic acid that stabilize Fe(III) reagents fail to support any substantial H_2O_2 -dependent Gif chemistry, despite the fact that some intriguing, but inert, ferric peroxo structures [7c] are generated in solution. In contrast, Fe(III) trifluoroacetate or picolinate reagents are rapidly reduced to Fe(II) species in the presence of H_2O_2 and as such can sustain catalytic turnover on equal footing to Fe(II) precatalysts. The only difference is that these Fe(III) reagents tend to afford higher amounts of oxygen- versus pyridine-trapped products compared with Fe(II) congeners, presum-

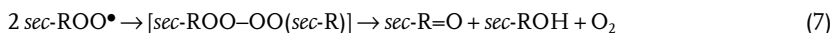
ably because of in-situ generation of increased levels of dioxygen. The important role of Fe(II) in the decomposition of sec alkyl hydroperoxides has also been demonstrated by Richens and co-workers [29], who were able to correlate the rate of ROOH decomposition to ketone with the rate of specific Fe(II) reagent assembly in Gif^{IV} chemistry. The reduction of ROOH to the corresponding alcohol was shown to be largely dependent on the efficiency of the heterogeneous reaction with Zn. Taken together, these observations are consistent with the typical role of the two major oxidation states of iron in mediating decomposition of ROOH (R = H, alkyl) under a Haber–Weiss–Walling mechanism [30].



Hydroxyl and substrate-derived alkoxy radicals, produced via Eq. (3), are the two main oxidants in Gif chemistry which are capable of effecting H-atom abstraction from unfunctionalized alkanes (Eq. 5). In contrast, Eq. (4) serves as a provider of Fe(II) ions and peroxy radicals, the latter being responsible for the increased amounts of dioxygen observed with Fe(III) reagents by virtue of disproportionation paths.



Under Gif conditions the resulting alkyl radicals enter into the competition indicated in Scheme 3 for *tert*- and *sec*-adamantyl radicals. Oxygen-rich environments favor the formation of alkylperoxy radicals, which after H-atom abstraction largely from H₂O₂ (Eq. 6) provide the initial oxo product of Gif chemistry, ROOH. In turn, ROOH undergoes metal-based decomposition (Eq. 3) and generates the substrate-centered alkoxy radicals noted above. Apparently, only *tert*-RO[•] are effective H-atom abstracting agents, leading to *tert*-ROH products, whereas *sec*-RO[•] radicals largely afford ketones, potentially via the 1,2-H atom shift step (Scheme 4). More ketone and *sec*-ROH (1:1) can also be provided via the bimolecular Russell reaction [31] (Eq. 7).



Under dioxygen-deficient conditions, pyridinium cations can compete with dioxygen in capturing alkyl radicals (Scheme 3). The resulting alkylpyridinium radical cations rapidly rearomatize by means of Fe(III)-induced oxidation to afford alkylpyridines and replenish the pool of Fe(II) sites. Other potential traps of alkyl radicals are Fe(III)–Cl moieties, which are known to effect oxidative chlorination (Eq. 8).



2.1.1.3 Scope and Limitations

Radical-based chemistry is considered to be nonselective in nature, but judicious choice of catalysts, substrates and reaction conditions, on the basis of information from relevant kinetics, can produce systems of synthetic utility [32] and biological significance [33]. As noted above, Gif oxygenation systems generate hydroxyl radicals, which, although indiscriminate in their action, can be rendered more selective by choosing substrates (for example DMSO) promoting high rate constants for HO• radical attack and by adjusting the concentration of the substrate. In the event of C–H activation, the resulting alkyl radicals usually have a wide range of reactivity/selectivity, and have frequently been employed in selective synthesis of C–C bonds [32].

By inspecting the typical Gif product profile noted in Scheme 1, the direct conversion of cyclohexane or cyclododecane to the corresponding ketone and alcohol stands out as an attractive industrial target. The one/2-ol mixture is an important feedstock for further catalytic oxidation (by HNO₃ or air) to adipic acid or 1,12-dodecanedioic acid, both of which are key precursors in the DuPont Nylon-manufacturing process [5]. The industrial oxidation of the cycloalkanes is mediated by alkane-soluble Co or Mn carboxylates operating at high temperatures (C₆H₁₂ 125–165 °C; C₁₂H₂₄ 150–160 °C) via radical Haber–Weiss autoxidation pathways. The mild Gif conversion of cyclohexane (35 %) to one/2-ol (almost quantitatively) can, in principle, be tuned to compete favorably with the industrial process, in which conversions are kept at low yields (10–13 %) to avoid overoxidation (one/2-ol selectivity 80–85 %). Furthermore, the enrichment of the one/2-ol feed with cyclohexanone, as observed in the Gif reaction, is considered beneficial at least for subsequent air-oxidation (Scientific Design process) of the one/2-ol mixture to adipic acid. However, as Schuchardt has noted [34], major limitations of the Gif reaction are:

- the relatively slow reaction rate (0.267 M solutions of one/2-ol with 100 % selectivity achieved in 1 h, compared with 0.3 M at 80 % selectivity in 40 min for the industrial process);
- the sizeable amount of catalyst needed and its quick hydrolysis to form particulate iron oxides/hydroxides; and
- the dependence on pyridine, an expensive and toxic solvent.

Among the other possible Gif products shown in Scheme 1, the oxidative transformation of pyridine to bipyridines and hydroxypyridines is of rather limited use, because of the formation of isomers that are not amenable to facile separation. Nevertheless, the reaction has precedence in the historic synthesis [35] of bipyridines via radical pyridine coupling mediated by FeCl₃ in the presence of Zn, but has been superseded by more selective coupling reactions that enable synthesis of unsymmetrically substituted bipyridines [36].

The synthesis of 2- and 4-functionalized pyridines, the most useful outcome of Gif chemistry, is based on selective addition of nucleophilic carbon-centered radicals at positions 2 and 4 of protonated pyridines. 2/4-Pyridyl moieties are regarded as high-value intermediates in the synthesis of compounds of industrial and phar-

macological importance [37]. The reaction has been studied in detail by Minisci [38], who has drawn attention to the superior rate constants for addition of alkyl radicals to pyridinium compared with pyridine, the increased selectivity for pyridyl positions 2 and 4 with increasing nucleophilicity of the alkyl radical, and the importance of solvent in determining the selectivity for 2- versus 4-pyridyl addition. Gif reactions produce alkyl radicals and are performed in acidified pyridine, hence the reaction is well suited for the production of 2- and 4-substituted pyridines, if the source of alkyl radicals has either equivalent C–H bonds or a tendency to react at specific C–H sites (for example with α -C–H bonds attached to heteroatoms). Otherwise, a more indirect approach can be implemented, as pioneered by Minisci [39], in which the reaction of HO• radicals with DMSO is harnessed to afford the reactive methyl radicals (Eq. 1); the latter can, in turn, abstract iodine from iodo-substituted substrates in a thermodynamically driven reaction (Eq. 9). Experimental procedures for both approaches are provided below.



Experimental

2-(1-Adamantyl)pyridine and 4-(1-Adamantyl)pyridine

Under an inert atmosphere (gas/vacuum line or Dry Box), iron(II) acetate (69.4 mg, 0.4 mmol) and picolinic acid (147.6 mg, 1.2 mmol) were dissolved in degassed pyridine/acetic acid (15.0/1.5 mL). 1-Iodoadamantane (1.05 g, 4 mmol) was then dissolved in this brown-red solution and degassed dimethylsulfoxide (8.0 mL) was added. Under a slow stream of argon flowing through the cooled solution (ice), a degassed aqueous solution (30 %) of hydrogen peroxide (1.65 mL, 15 mmol) was added dropwise over a period of 15 min, and the reaction was stirred for an additional 30 min at room temperature. The progress of the reaction can be followed by GC–FID (SPB-1 column; typical temperature program: initial temperature = 50 °C, hold temperature for 9 min, increase temperature by 3 ° min^{−1} to 135 °C, thereafter by 5 ° min^{−1} to the final temperature of 260 °C; indicative retention times (min): 1-Ad-OH 29.4, 1-Ad-I 39.9, 2-(1-Ad)py 52.9, 4-(1-Ad)py 56.1). At the end of the reaction, the reaction solution was rendered basic (20 % NaOH) and extracted with diethyl ether (3 × 50 mL). The ether extracts were dried over sodium sulfate and evaporated to provide a residue which was further purified by silica gel chromatography (ether/hexane) to afford the title compounds. 1-Adamantanol (0.097 g, 0.63 mmol, 15.7 %) and trace amounts of unreacted 1-iodoadamantane were also recovered. 2-(1-Adamantyl)pyridine (0.381 g, 1.78 mmol, 44.5 %): m.p. 36–38 °C. IR (KBr, cm^{−1}) 3050, 2914, 2848, 1583, 1458. UV–visible (ethyl acetate) λ_{max} 262 nm. ¹H NMR (400 MHz, CDCl₃) 8.56 (ddd, J = 4.76, 2.02, 0.92 Hz, 1H), 7.61 (td, J = 7.74, 1.84 Hz, 1H), 7.26 (t, J = 1.10 Hz, 1H), 7.07 (ddd, J = 7.42, 4.76, 1.10 Hz, 1H), 2.10 (br. s, 3H), 1.98 (br. d, 6H), 1.78 (br. d, 6H). ¹³C NMR (400 MHz, CDCl₃) 168.9, 148.7, 136.2, 120.8, 118.2, 41.8, 36.7, 28.8. MS (EI) m/z 213 (100, [M]⁺). 4-(1-Adamantyl)pyridine (0.293 g,

1.37 mmol, 34.2%): m.p. 75–77 °C. IR (KBr, cm^{-1}) 3077, 3028, 2914, 2843, 1589. UV–visible (ethyl acetate) λ_{max} 256 nm. ^1H NMR (400 MHz, CDCl_3) 8.51 (dd, $J = 4.76, 1.65$ Hz, 2H), 7.28 (dd, $J = 4.76, 1.65$ Hz, 2H), 2.10 (br. s, 3H), 1.87 (br. d, 6H), 1.76 (m, 6H). ^{13}C NMR (400 MHz, CDCl_3) 160.1, 149.8, 120.5, 42.5, 36.8, 28.9. MS (EI) m/z 213 (100, $[\text{M}]^+$).

2-Cyclohexylpyridine and 4-cyclohexylpyridine

Under an inert atmosphere (gas/vacuum line or Dry Box), iron(II) acetate (69.4 mg, 0.4 mmol) and picolinic acid (147.6 mg, 1.2 mmol) were dissolved in degassed pyridine/acetic acid (15.0/1.5 mL) and cyclohexane (1.0 mL, 11.9 mmol). Under a slow stream of argon flowing through the cooled solution (ice), a degassed aqueous solution (30 %) of hydrogen peroxide (2.20 mL, 20 mmol) was added dropwise over a period of 30 min, and the reaction was stirred for an additional 2 h at room temperature. The progress of the reaction can be followed by GC–FID (indicative retention times (min): Cy 2.9, Cy–OH 8.1, Cy=O 8.3, 2-(Cy)py 35.2, 4-(Cy)py 39.0). At the end of the reaction, the reaction solution was rendered basic (20 % NaOH) and extracted with diethyl ether (3 \times 50 mL). The diethyl ether layer was dried over sodium sulfate and evaporated to provide a residue which was further purified by silica gel chromatography (ether/hexane) to afford the title compounds as oily substances. 2-Cyclohexylpyridine (56 mg, 0.348 mmol, 2.9%): IR (CHCl_3 , cm^{-1}) 3023, 2930, 2849, 1220. UV–visible (ethyl acetate) λ_{max} 264 nm. ^1H NMR (400 MHz, CDCl_3) 8.49 (ddd, $J = 4.77, 1.83, 0.91$ Hz, 1H), 7.55 (td, $J = 7.51, 1.83$ Hz, 1H), 7.11 (dt, $J = 7.87, 0.92$ Hz, 1H), 7.04 (ddd, $J = 7.50, 4.92, 1.10$ Hz, 1H), 2.66 (tt, $J = 11.73, 3.39$ Hz, 1H), 2.00–1.20 (m, 10H). ^{13}C NMR (400 MHz, CDCl_3) 166.7, 149.2, 136.4, 121.8, 120.8, 47.0, 33.1, 29.9, 26.7. MS (EI) m/z 161 (61, $[\text{M}]^+$), 106 (100). 4-Cyclohexylpyridine (17 mg, 0.106 mmol, 0.9%): IR (CHCl_3 , cm^{-1}) 3017, 2936, 2854, 1220. UV–visible (ethyl acetate) λ_{max} 258 nm. ^1H NMR (400 MHz, CDCl_3) 8.47 (dd, $J = 4.48, 1.65$ Hz, 2H), 7.11 (dd, $J = 4.48, 1.65$ Hz, 2H), 2.47 (m, 1H), 1.90–1.20 (m, 10H). ^{13}C NMR (400 MHz, CDCl_3) 157.2, 149.5, 122.7, 44.1, 33.7, 29.9, 26.4. MS (EI) m/z 161 (100, $[\text{M}]^+$).

Acknowledgments

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2.1.2

Oxidation of Unactivated Alkanes by Dioxiranes

Waldemar Adam and Cong-Gui Zhao

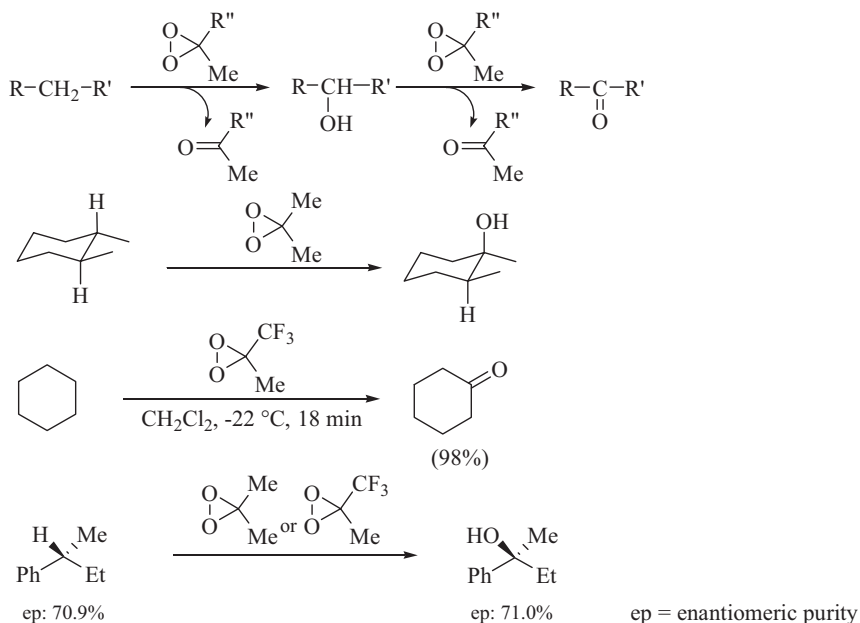
2.1.2.1 Introduction and Fundamental Examples

The C–H oxidation of unactivated alkanes is the most direct method of introducing oxygen functional groups in alkanes. Such oxyfunctionalization, especially

when enantioselective, plays an important role in biological systems in which oxidizing enzymes (monooxygenases and dioxygenases) catalyze the C–H insertion directly with molecular oxygen [1, 2]. Dioxiranes are currently the only readily available nonmetallic organic oxidants capable of directly oxyfunctionalizing sp^3 -hybridized C–H bonds.

Historically, the unusual oxidizing power of the three-membered-ring cyclic peroxides was demonstrated for dimethyldioxirane (DMD) under in-situ conditions [3]; subsequently, its isolation was achieved by distillation [4]. The ease of preparation and ready access of dilute (<0.10 M) acetone solutions of DMD constitute a major breakthrough, which revolutionized dioxirane chemistry, as witnessed by the numerous reviews on this subject [5–19].

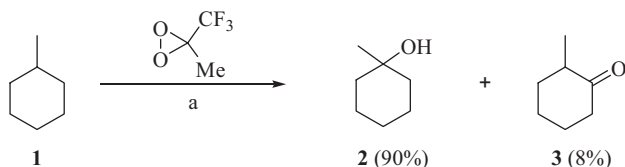
DMD is suitable for the oxidation of most substrates; with substances that are resistant to oxidation, however, the more reactive but also more expensive methyl(trifluoromethyl)dioxirane (TFD) is necessary. The oxidation is stereoselective for both dioxiranes and proceeds with complete retention of configuration at the oxidized carbon atom (Scheme 1) [20–22]. The reactivity follows the usual order of electrophilic oxidation – primary < secondary < tertiary < benzylic < allylic C–H bonds. Except for tertiary C–H bonds, which produce the oxidatively inert tertiary alcohols, further oxidation of the primary product (an alcohol) to a ketone or aldehyde (the latter is readily further oxidized to the corresponding acid) is possible, because the α -hydrogen of the alcohol is usually more reactive than that of the unactivated alkane, especially for allylic C–H bonds.



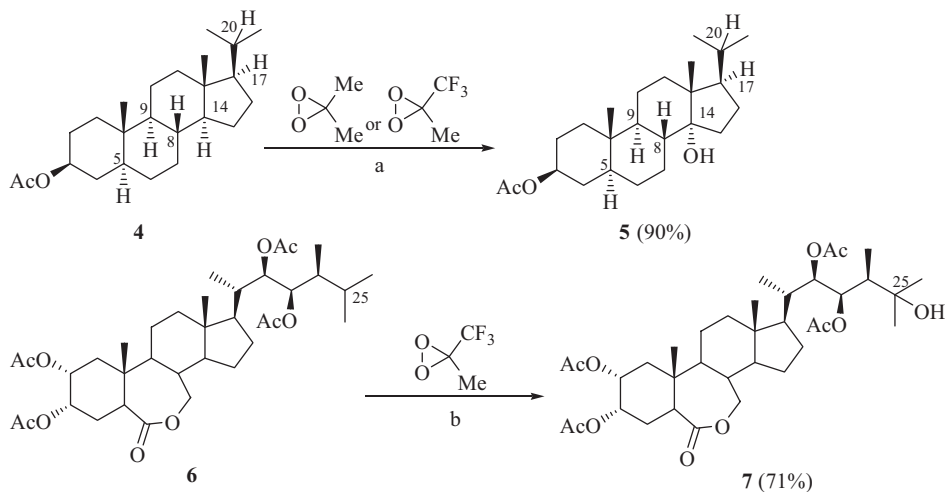
Scheme 1. C–H Insertions by dimethyldioxirane (DMD) and methyl(trifluoromethyl)dioxirane (TFD).

Although the α -hydrogen atoms in alcohols are very reactive, those of ethers and particularly esters are substantially more sluggish toward oxidation than those of alcohols. Thus, the overoxidation of primary and secondary alcohols may be prevented by protection of the newly formed hydroxy group by in-situ acylation with trifluoroacetic anhydride [23]. Preparatively most significant, the C–H bonds adjacent to carbonyl (ketone, aldehyde, ester, and amide) and cyano groups are inert towards DMD and even TFD oxidation.

The regioselectivity of the C–H insertion is mainly controlled by the reactivity of the C–H bonds. For example, in the DMD oxidation of *trans*-dimethylcyclohexane [24] the tertiary C–H bond is selectively oxidized rather than the secondary bonds (Scheme 1). Similarly, when methylcyclohexane (**1**) is oxidized by TFD, the alcohol **2** (oxidation at the tertiary C–H bond) prevails, as shown in Scheme 2. When the reactivity is similar, the regioselectivity is governed by steric factors. This is well illustrated in Scheme 3 for the steroid pregnane (**4**), which, for steric reasons, is selectively hydroxylated at the C₁₄ position in the presence of other tertiary C–H bonds (C₅, C₈, C₉, C₁₇, C₂₀) [25]. Similarly, in the TFD oxidation of brassinolide (**6**), only the tertiary C–H bond of the side-chain (position 25) is hydroxylated (Scheme 3) [26].

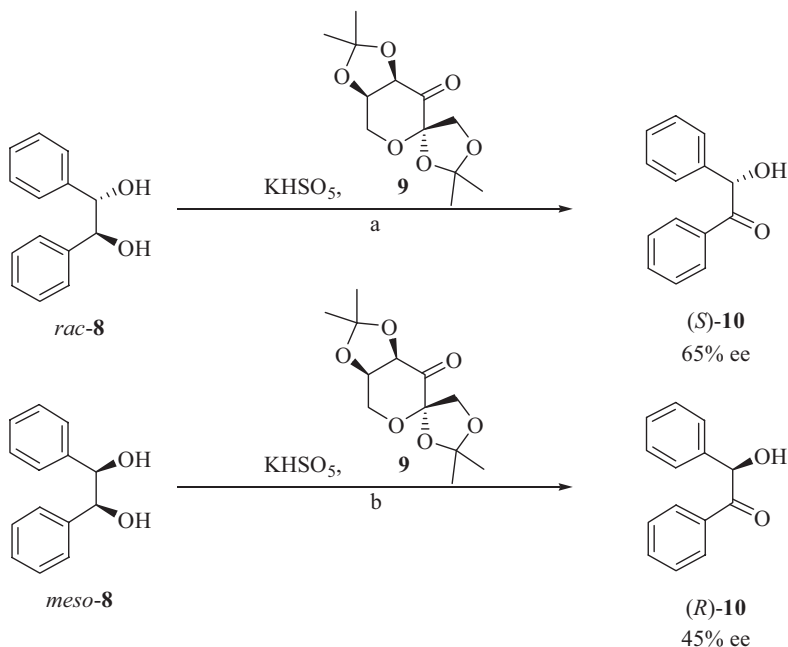


Scheme 2. Regioselective C–H insertion: (a) CH₂Cl₂/tri-fluoroacetone (9:1), initial [TFD] ca. 0.5 M, -22 °C, 8 min.



Scheme 3. Regioselective C–H oxidation of steroids:
(a) conditions not given, 40 % conversion;
(b) TFD (1.2 equiv.), CH₂Cl₂/TFP, rt, dark, N₂, 2 days.

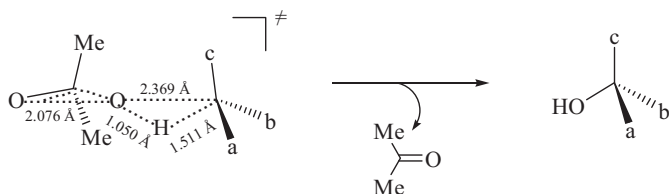
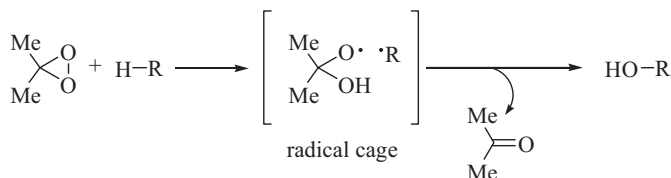
Enantioselective C–H insertion is still a virgin area in dioxirane chemistry, but its feasibility has been demonstrated in the kinetic resolution of racemates and in the desymmetrization of meso 1,2-diols and their acetals. Moderately good enantioselectivity has been achieved by use of Shi's ketone **9** as the precursor to the dioxirane (Scheme 4) [27, 28].



Scheme 4. Enantioselective C–H oxidation of vic diols: (a) Kinetic resolution, 1.5:1 $\text{CH}_3\text{CN}/\text{Na}_2\text{B}_4\text{O}_7$, buffer (pH 10.5), K_2CO_3 , 0°C , 3 h, 51 % conversion; (b) desymmetrization, 1.5:1 $\text{CH}_3\text{CN}/\text{Na}_2\text{B}_4\text{O}_7$, buffer (pH 10.5), K_2CO_3 , 0°C , 3 h, 89 % conversion.

2.1.2.2 Mechanism

A concerted, spiro-structured, oxenoid-type transition state has been proposed for C–H oxidation by dioxiranes (Scheme 5). This mechanism is based mainly on the stereoselective retention of configuration at the oxidized C–H bond [20–22], but also kinetic studies [29], kinetic isotopic effects [24], and high-level computational work support the spiro-configured transition structure [30–32]. The originally proposed “oxygen-rebound” mechanism [24, 33] was recently revived in the form of so-called molecule-induced homolysis [34, 35]; however, such a radical-type process has been experimentally [36] and theoretically [30] rigorously discounted.

Concerted Oxenoid Mechanism**"Oxygen-Rebound" Mechanism**

Scheme 5. The concerted oxenoid versus the stepwise oxygen-rebound mechanism for the C–H oxidation by dioxiranes.

2.1.2.3 Scope and Limitations


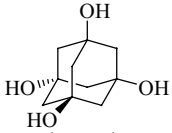
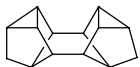
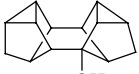
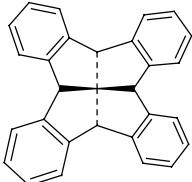
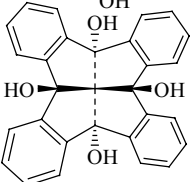
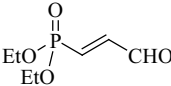
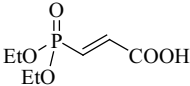
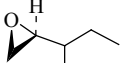
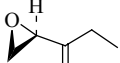
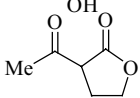
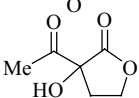
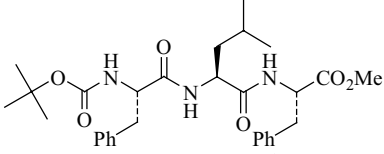
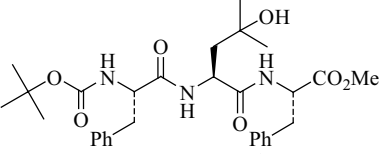
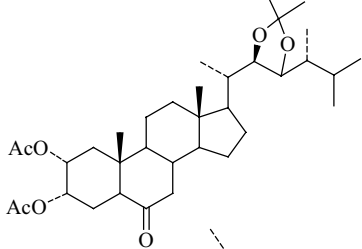
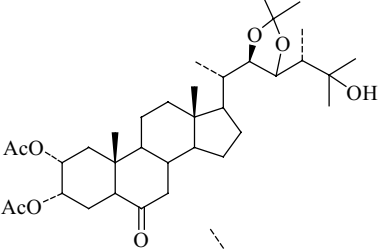
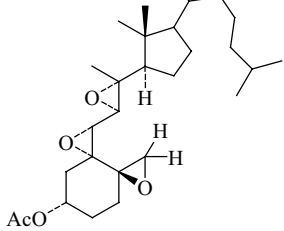
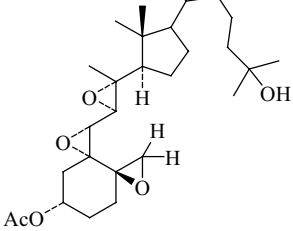
With either isolated or in-situ-generated DMD or TFD, numerous substrates with different types of C–H bond have been oxyfunctionalized. Some typical examples, mostly hydroxylations, are summarized in Table 1.

For most of these operations, isolated dioxirane solutions are more convenient, because simpler work-up procedures are involved. Furthermore, hydrolytically and acid/base-sensitive substrates may be employed, because the reaction is conducted under strictly anhydrous and neutral conditions. Solvents inert toward dioxirane oxidation may be used for dilution purposes in these oxidations, which include acetone, butanone, cyclohexanone, CH_2Cl_2 , CHCl_3 , CCl_4 , benzene, and CH_3CN . Alcohols (except *t*-BuOH) and ethers normally should be avoided as solvents, because they react slowly with dioxiranes, especially TFD [37].

The required ketone solutions of the dioxiranes (usually DMD and TFD) may be prepared by distillation (slightly reduced pressure, ca. 100 torr for DMD; 650 torr for TFD) directly from the ketone/monoperoxysulfate mixture used for the dioxirane generation. For less volatile dioxiranes (e.g. cyclohexanone dioxirane), the “salting-out” technique may be employed [38]. “Ketone-free” dioxirane solutions (both DMD [39] and TFD [40]) may be obtained by diluting the originally distilled ketone solution of the dioxirane with the solvent of choice (usually CH_2Cl_2 or CCl_4 ; must not be miscible with water), followed by extraction of the ketone with several washes of aqueous buffer solution.

The disadvantages of using isolated dioxirane solutions for oxidations are mainly the low dioxirane concentrations (<0.1 M) and the poor dioxirane yield (ca. 5–10% based on monoperoxysulfate) that may be obtained, and the fact that such

Table 1. Illustrative examples of dioxirane-mediated C–H insertions.

Starting material	Product	Yield (%)	Ref.
		73	[41]
		98	[42]
		56	[43]
		100	[44]
		90	[29]
		98	[45]
		49	[46]
		62	[26]
		82	[47]

oxidations are stoichiometric and not catalytic. Such oxidations are thus limited to small-scale (up to 50 mmol) laboratory applications.

When the substrate is hydrolytically robust, the in-situ mode is recommended, because under these conditions the reaction is in principle catalytic with respect to the ketone and may be readily scaled up. As for effective in-situ conditions, the current practice is to operate in homogeneous media (water-miscible organic solvents [48]) and in a moderately alkaline pH buffer (ca. 8–10 [49]), which is preferred to the originally recommended biphasic system (water-immiscible organic solvent) and neutral pH buffer (ca. 7–8) [3]. Although acetone and trifluoroacetone are usually employed as ketone catalysts, basically any ketone may be used if it is sufficiently oxidatively resistant and has a reactive enough carbonyl group. A highlight of this is the recent development of enantioselective oxidations [5–10] employing optically active ketones in the in-situ mode.

Acetonitrile is the solvent of choice for in-situ C–H oxidation. Although ethereal solvents, for example dimethoxymethane, 1,2-dimethoxyethane, 1,4-dioxane, and mixtures thereof, have been successfully used for dioxirane-mediated catalytic asymmetric epoxidations, their application in in-situ C–H oxidation has not been vigorously established.

The chemoselectivity of the dioxirane oxyfunctionalization usually follows the reactivity sequence heteroatom (lone-pair electrons) oxidation > π -bond epoxidation > C–H insertion, as expected of an electrophilic oxidant. Because of this chemoselectivity order, heteroatoms in a substrate will be selectively oxidized in the presence of C–H bonds and even C–C double bonds. In allylic alcohols, however, C–H oxidation of the allylic C–H bond to α,β -unsaturated ketones may compete efficaciously with epoxidation, especially when steric factors hinder the dioxirane attack on the π bond. To circumvent the preferred heteroatom oxidation and thereby alter the chemoselectivity order in favor of the C–H insertion, tedious protection methodology must be used. For example, amines may be protected in the form of amides [46], ammonium salts [50], or BF_3 complexes [51]; however, much work must still be expended on the development of effective procedures which avoid the oxidation of heteroatoms and C–C multiple bonds.

Because C–H bonds are usually less reactive towards dioxirane oxidation than heteroatoms and C–C multiple bonds, it is instructive to give a few general guidelines on the compatibility of functional groups within the substrate to be submitted to oxidative C–H insertion: Substances with low-valent heteroatoms (N, P, S, Se, I, etc.), C–C multiple bonds, and $\text{C}=\text{X}$ groups (where X is a N or S heteroatom) are normally not suitable for C–H insertions, because these functionalities react preferably. Even heteroarenes are more susceptible to dioxirane oxidation than C–H bonds, whereas electron-rich and polycyclic arenes are only moderately tolerant, but electron-poor arenes usually resist oxidation by dioxiranes. N-oxides and N-oxyl radicals are not compatible because they catalyze the decomposition of the dioxirane. Oxygen insertion into Si–H bonds by dioxirane is more facile than into C–H bonds and, therefore, silanes are not compatible. Substance classes normally resistant towards dioxirane oxidation include the carboxylic acids and their derivatives (anhydrides, esters, amides, and nitriles), sulfonic acids and their de-

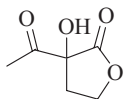
rivatives, phosphonic acids and their derivatives, ammonium salts, ketones, epoxides, sulfones, nitro compounds, halogen (F, Cl, Br) compounds, and tetra-substituted silanes and stannanes. The synthetically valuable C–H bonds adjacent to carbonyl (ketones, aldehydes, esters and amides) and cyano groups resist dioxirane oxidation whereas the C–H bonds next to an ether-type oxygen atom and C–H bonds flanked by two electron-withdrawing groups (e.g. 1,3-diketones) are only marginally resistant; C–H bonds next to hydroxy groups in alcohols must be avoided, however. The aldehyde C–H bond and the N–H bond in non-tertiary ammonium salts react with dioxiranes only sluggishly and are moderately compatible.

Experimental

Preparation of a DMD Solution in Acetone [52]

(This is a simplified procedure originally reported by Murray et al. [4, 53].) A 4-L, three-necked, round-bottomed reaction flask was equipped with an efficient mechanical stirrer and an addition funnel for solids, the latter connected by means of a U tube (i.d. 25 mm) to a 250-mL receiving flask with an outlet which was attached to a water pump. The receiving flask was cooled to -78°C by means of a dry ice/acetone bath, whereas the reaction flask was kept at $5\text{--}10^{\circ}\text{C}$ by means of an ice/water bath and charged with a mixture of water (254 mL), acetone (192 mL), and NaHCO_3 (58.0 g). With vigorous stirring and cooling at $5\text{--}10^{\circ}\text{C}$, solid Caroate (120 g, 0.195 mol) was added in five portions at 3-min intervals. Three minutes after the last addition, a moderate vacuum (80–100 mmHg) was applied, the cooling bath was removed from the reaction flask, and, while the contents were stirred vigorously, the DMD/acetone mixture was distilled (150 mL, 0.09–0.13 M, ca. 8% yield) by collecting it in the cooled (-78°C) receiving flask. The DMD acetone solution was dried over molecular sieves (4 \AA) and its concentration was determined most conveniently by measuring the characteristic dioxirane absorbance at $\lambda_{\text{max}}\ 325\text{ nm}$ ($\epsilon\ 12.5 \pm 0.5\ \text{M}^{-1}\text{cm}^{-1}$). This DMD solution may be stored in the freezer (-20°C) for several months without appreciable decomposition.

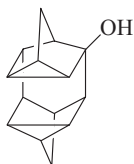
3-Acetyl-3-hydroxyoxacyclopentan-2-one [45]



The DMD acetone solution (0.07 M, 14.0 mL, 1.0 mmol) was added rapidly while stirring at room temperature (ca. 20°C) to 3-acetyloxacyclopentan-2-one (128 mg, 1.0 mmol), and stirring of the mixture was continued for 24 h at room temperature. Another equivalent of DMD solution was then added and stirring was continued for 24 h. This procedure was repeated until complete conversion of the sub-

strate (monitored by TLC, a total of 41 mL of DMD solution was consumed). The solvent was removed under reduced pressure (20 °C/20 torr) and the title compound was obtained as a colorless oil (142 mg, 98 %). IR (CCl₄): ν (cm⁻¹) = 3600–3300, 3000, 2930, 1800, 1740, 1550, 1385, 1365, 1210, 1170, 1150, 1110; ¹H NMR (CDCl₃, 250 MHz): δ (ppm) = 2.30 (s, 3 H), 2.29–2.41 (m, 1H), 2.64 (ddd, 1H, J = 13.6, 7.2, 4.5 Hz), 4.30–4.60 (m, 3 H); ¹³C NMR (CDCl₃, 63 MHz): δ (ppm) = 24.6 (q), 33.9 (t), 66.1 (t), 81.2 (s), 174.2 (s), 205.0 (s); MS (70 eV): m/z (%) = 128 (0.4), 127 (0.4), 102 (32), 72 (2), 58 (2), 57 (16), 56 (32), 44 (14), 43 (100), 42 (10).

(±)-Heptacyclo[8.4.0.0^{2,7}.0^{3,5}.0^{4,8}.0^{9,13}.0^{12,14}]tetradecan-1-ol [54]



The Caroate (2KHSO₅·KHSO₄·K₂SO₄, 600 g, 976 mmol), dissolved in water (800 mL), was added slowly over a 2-h period to a cooled (ice bath), well-stirred mixture of Binor S [heptacyclo(8.4.0.0^{2,7}.0^{3,5}.0^{4,8}.0^{9,13}.0^{12,14})tetradecane] (20.0 g, 108.5 mmol, recrystallized from an ethanol/ether mixture), acetone (300 mL), dichloromethane (200 mL), sodium bicarbonate (280 g), and water (300 mL). After complete addition, the reaction mixture was left to reach room temperature and stirred for an additional 12 h. The solids were removed by filtration and washed with dichloromethane (2 × 200 mL). The filtrate and washes were transferred to a separatory funnel to separate the dichloromethane layer. This phase was washed with water and saturated brine and then dried (Na₂SO₄). After evaporation of the solvent at reduced pressure (ca. 15 torr), the residue was chromatographed on silica gel. On elution with pentane, the unreacted starting material (12.2 g) was recovered; elution with ether–pentane, 3:7, then gave the acetate of the title compound (650 mg, 2 %); further elution gave the title alcohol as white plates (7.7 g, 98 % based on consumed starting material), m.p. 153–154 °C. IR (KBr): ν (cm⁻¹) = 3332, 3270, 3070, 3058, 2928, 2905, 2857, 1296, 1101, 1083, 799, 789; ¹H NMR (CDCl₃, 400 MHz): δ (ppm) = 1.12 (t, J = 5.6 Hz, 1 H), 1.17 (m, 2 H), 1.22 (t, J = 5.8 Hz, 1 H), 1.26 (m, 1 H), 1.29 (m, 1 H), 1.37 (q, J = 10 Hz, 2 H), 1.44 (d, J = 11 Hz, 1 H), 1.51 (br s, 1 H), 1.61 (br s, 1 H), 1.78 (d, J = 9 Hz, 1 H), 1.83 (br s, 1 H), 1.90 (br s, 1 H), 1.94 (br s, 2 H); ¹³C NMR (CDCl₃, 100 MHz): δ (ppm) = 15.4; (d, J = 174 Hz), 16.1 (d, J = 172 Hz), 16.8 (d, J = 174 Hz), 17.0 (d, J = 175 Hz), 19.0 (d, J = 175 Hz), 22.7 (d, J = 175 Hz), 31.3 (t, J = 132 Hz), 32.1 (d, J = 146 Hz), 33.0 (t, J = 131 Hz), 38.0 (d, J = 146 Hz), 39.6 (d, J = 137 Hz), 39.7 (d, J = 137 Hz), 49.8 (d, J = 136 Hz), 83.2 (s); MS (70 eV): m/z (%) = 200 (20), 134 (100), 118 (65), 82 (30).

(S)-2-Hydroxy-1,2-diphenylethanone [(S)-10] [28]

Na₂B₄O₇ (0.05 M, 1.0 mL) in 4 × 10⁻⁴ M aqueous Na₂EDTA was added to a solution of *d,l*-hydrobenzoin (*rac*-8, 21.4 mg, 0.10 mmol), ketone 9 (77.5 mg, 0.30 mmol),

and Bu_4NHSO_4 (1.5 mg, $4.0\ \mu\text{mol}$) in 1.5 mL CH_3CN while stirring at ca. $0\text{--}5^\circ\text{C}$ (ice bath). A solution of Caroate (46.0 mg, $0.075\ \text{mmol}$) and K_2CO_3 (44.0 mg, $0.315\ \text{mmol}$) in 0.33 mL $4\times 10^{-4}\ \text{M}$ aqueous Na_2EDTA were added simultaneously by means of separate syringes over a period of 2 h. The mixture was further stirred for 1 h, diluted with water (20 mL), extracted with ether ($3\times 20\ \text{mL}$), washed with water ($2\times 10\ \text{mL}$), and dried over MgSO_4 . After evaporation of the solvent ($20^\circ\text{C}/20\ \text{torr}$), the residue was submitted to silica-gel chromatography, to afford the ketone **9** (40–60 % yield) and the title product (*S*)-**10** (10.3 mg, 51 % conversion, 95 % yield). For the latter an ee value of 65 % was determined by HPLC analysis on a Chiralcel OD-H column. ^1H NMR (CDCl_3 , 200 MHz): δ (ppm) = 4.60 (s, 1 H), 5.91 (s, 1H), 7.19–7.68 (m, 10H).

Acknowledgments

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2.1.3

Selective Enzymatic Hydroxylations

Bruno Bühler and Andreas Schmid

2.1.3.1 Introduction

Enzymes are valuable catalysts in organic synthesis because of their often unique features:

- highly selective operation in complex reaction mixtures;
- the virtual absence of side reactions leading to simpler separation processes and higher yields; and
- savings in energy and waste treatment costs owing to mild reaction conditions.

Numerous oxidoreductases enable highly chemo-, regio-, and enantioselective oxyfunctionalization of readily available petrochemicals, xenobiotics, and larger molecules such as steroids under mild conditions (ambient temperature and pressure with water as the solvent).

Figure 1 shows a simplified tree of oxidoreductase classes with a focus on enzymes capable of oxyfunctionalizing sp^3 -hybridized carbon atoms. This tree will lead through this chapter, which concentrates on mechanistic and application aspects of C–H activation. Considering the first level of the tree, such reactions are mainly catalyzed by oxygenases and peroxidases. Oxidases and dehydrogenases have also been reported to catalyze the hydroxylation of benzylic and allylic C–H bonds. Dehydrogenases use water as oxygen donor. Examples are 4-cresol dehydrogenase found in *Pseudomonas putida* strains or denitrifying bacteria [1, 2] and ethylbenzene dehydrogenase of *Azoarcus*-like strains initiating, interest-

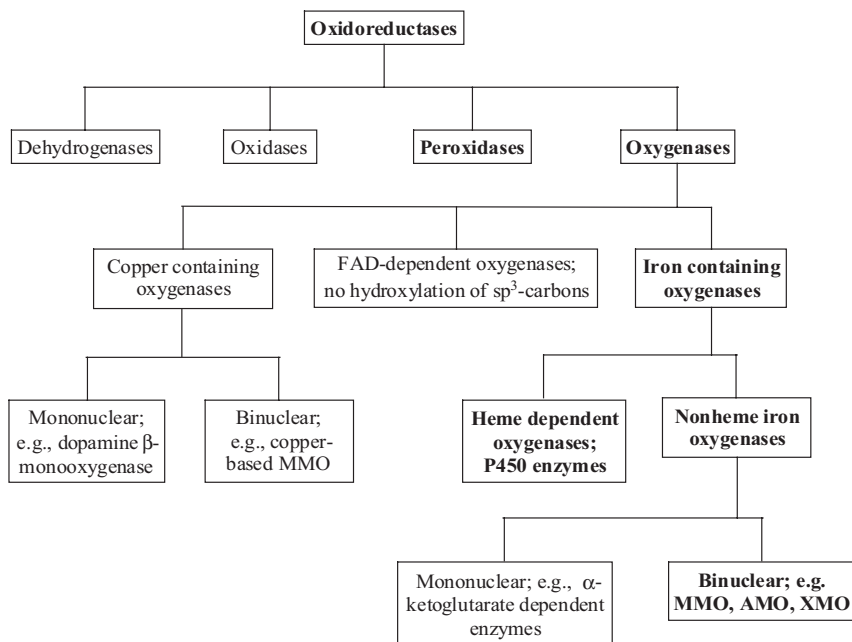


Figure 1. Classification of oxidoreductases with a focus on enzymes capable of sp^3 -carbon oxyfunctionalization. MMO, methane monooxygenase; AMO, alkane monooxygenase; XMO, xylene monooxygenase. The most prominent enzyme classes in respect of sp^3 -carbon oxyfunctionalization are shown in bold.

ingly, an anaerobic catabolic pathway [3–5]. The two enzymes catalyze the oxidation of 4-cresol to 4-hydroxybenzaldehyde and ethylbenzene to (*S*)-1-phenylethanol, respectively. 4-Cresol dehydrogenase requires azurin or nitrate as physiological electron acceptors whereas the natural electron acceptor of ethylbenzene dehydrogenase is not yet known.

Oxidases couple the one-, two-, or four-electron oxidation of substrates to the two- or four-electron reduction of dioxygen to hydrogen peroxide or to water. Because oxygen from molecular oxygen is not introduced into the substrate, hydroxylations are not typical of oxidases. Vanillyl-alcohol oxidase from *Penicillium simplicissimum*, for instance, catalyzes both the benzylic desaturation and the benzylic hydroxylation of *para*-alkylphenols, however, depending on the nature of the aliphatic side chain [6, 7]. The mechanisms include *para*-quinone methides as common intermediates and differ in whether water attacks the methide or not. Thus, the introduced oxygen atom is derived from water, as observed with hydroxylating dehydrogenases.

The classical peroxidase reaction consists of one-electron oxidation of the substrate, with hydrogen peroxide or organic peroxides as electron acceptors. Peroxidases also catalyze a large variety of oxygen-transfer reactions including olefin

epoxidations, sulfoxidations, and allylic, propargylic, and benzylic hydroxylations; but no aliphatic hydroxylations have yet been reported [8–10]. In such two-electron oxidations a peroxide serves as oxygen donor and one molecule of water (or alcohol, for organic peroxide-driven reactions) is produced as a co-product. An advantage of peroxidases is that they need no regeneration of cofactors such as NAD(P)H. A major shortcoming is, however, the low operational stability of peroxidases, usually as a result of peroxide-induced deactivation. An example is the facile oxidative deterioration of the porphyrin ring in heme-dependent peroxidases, for example the frequently used chloroperoxidase, necessitating the maintenance of low hydrogen peroxide concentrations and/or the in-situ generation of hydrogen peroxide from molecular oxygen with a chemical reductant or an oxidase [11–13].

Oxygenases, which derive the oxygen atom introduced into the C–H bonds from molecular oxygen, can be found in almost all kinds of living cells, from bacterial to mammalian. These enzymes have important physiological roles in detoxification (e.g. in mammalian liver cells), in the biosynthesis of secondary metabolites, hormones, signaling molecules, and many other compounds, and in hydrocarbon degradation by bacteria. Because of the high flexibility needed for detoxification and, especially, degradation of hydrocarbons and xenobiotics, oxygenases catalyze a huge variety of oxyfunctionalizations, also including aliphatic hydroxylations, and have high potential for preparative applications [14, 15]. The high abundance and versatility of oxygenases, their ability to specifically introduce oxygen from molecular oxygen, and the absence of enzyme-destabilizing peroxides as reactants have led to considerable advances in process implementation and to the first examples of industrial processes. Enzymatic oxygenations of interest for industrial applications include hydroxylations of alkyl, allyl, or benzyl carbon atoms (C–H activation at sp^3 -hybridized carbon atoms), vinyl group epoxidations and aromatic (di)oxygenations (oxygenation of sp^2 -hybridized carbon atoms), Baeyer–Villiger oxidations, and heteroatom oxygenations. Several excellent reviews with comprehensive coverage of the literature on oxygenase catalyzed reactions have appeared in journals and text books [16–34]. Most published biocatalytic processes for preparative hydrocarbon oxyfunctionalization include oxygenase-catalysis, on which we focus in this chapter.

2.1.3.2 Mechanisms of Oxygenase Catalysis

As shown in Fig. 1, the main oxygenase classes include FAD-, copper-, and iron-dependent enzymes. FAD-dependent oxygenases are known to catalyze epoxidations, aromatic oxygenations, Bayer–Villiger oxidations, and heteroatom oxygenations, but no oxyfunctionalizations of sp^3 -hybridized carbon atoms. In contrast, copper-containing oxygenases such as the mononuclear dopamine β -monooxygenase and the binuclear copper-based methane monooxygenase catalyze the hydroxylation of C–H bonds [35–37]. However, the most abundant and best-studied oxygenases catalyzing C–H oxyfunctionalizations are iron-containing enzymes, on which we concentrate in the following section. Iron-containing oxygenases can be divided in two categories: heme monooxygenases and nonheme iron oxygenases (Fig. 1).

2.1.3.2.1 Heme-dependent Oxygenases

Heme monooxygenases harbor a protoporphyrin IX tetrapyrrole system containing one catalytic iron nucleus; the resulting prosthetic group is designated a heme group. The iron is coordinated by four nitrogen atoms, one from each pyrrole ring, and has two coordination sites left. The ligands occupying these coordination sites and the surrounding protein structure that defines the electronic and steric environment of the heme group convey the typical catalytic activity spectrum on the enzymes.

Such heme monooxygenases usually belong to the class of cytochrome P450 enzymes. Cytochrome P450 monooxygenases catalyze diverse reactions ranging from participation in the biosynthesis of hormones in animals and secondary metabolites in plants to the biodegradation of xenobiotic compounds. Furthermore, P450 enzymes ensure detoxification of exogenous compounds by rendering these mostly lipophilic compounds water-soluble, thus facilitating their excretion. Because of this essential function, mammalian cytochrome P450 monooxygenases have been thoroughly studied in the context of drug metabolism [38–40]. Increasing attention is being devoted to microbial P450 monooxygenases and, in particular, to their application for biotransformations [34, 41–43]. Bacterial cytochrome P450 enzymes tend to be soluble (class I) whereas the eucaryotic enzymes tend to be membrane associated (class II) [44].

Most of the cytochrome P450 systems reported to date are multicomponent enzymes with additional proteins for transport of reducing equivalents from NAD(P)H to the terminal cytochrome P450 component. Typical electron-transfer chains of class I P450 systems (bacterial or from mammalian adrenal mitochondria, soluble P450) consist of a ferredoxin reductase and a ferredoxin, whereas class II P450 systems (mammalian hepatic drug-metabolizing isoforms, membrane bound P450) include a flavin containing P450 reductase. An exception is cytochrome P450 BM-3 of *Bacillus megaterium* which consists of a single soluble polypeptide with a P450 domain and an electron transport domain of the microsomal type (class II) [45, 46]. The fusion-based efficiency of electron transfer in cytochrome P450 BM-3 provides this enzyme with the highest catalytic activity known for P450 monooxygenases ($\sim 285 \text{ s}^{-1}$ NADPH oxidation activity with arachidonate) [47].

Several crystal structures of microbial cytochrome P450 enzymes are now available [45, 48–50]. The first X-ray structure for P450 was that of cytochrome P450_{cam} [48], which was isolated from *P. putida* and catalyzes the 5-exo hydroxylation of its natural substrate D-camphor to 5-exohydroxycamphor. The P450_{cam} enzyme has served as a model system for general studies of cytochrome P450 enzymes in terms of structure, function, and mechanism [48, 51]. The heme group of P450 monooxygenases is directly involved in the oxidation process by activating molecular oxygen. The catalytic cycle by which cytochrome P450-mediated hydroxylation occurs has been intensively studied [40, 51–55]. Figure 2 shows the various intermediate species formed in P450 reactions.

The resting iron(III) enzyme binds substrate reversibly, resulting in a decrease in the reduction potential of iron. An electron is transferred from NAD(P)H via

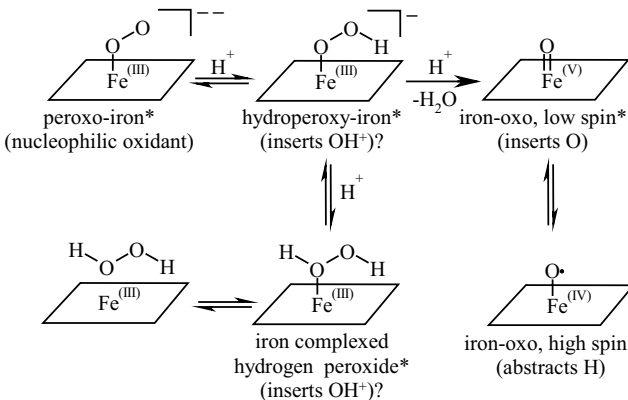


Figure 2. Intermediate species formed in P450 reactions. The parallelogram represents heme. *Proposed roles of iron–oxygen intermediates as oxidants. Adapted from [52].

the electron-transfer chain to P450 to give an iron(II) species. Reversible binding of oxygen then occurs to give the superoxide-iron complex. A second reduction reaction gives the peroxy-iron species where oxygen is in the formal oxidation state of hydrogen peroxide. Protonation of the peroxy-iron species on the distal oxygen gives the hydroperoxy-iron intermediate. A second protonation on the distal oxygen and water abstraction results in the iron-oxo species, regarded as the consensus oxidizing species 10 years ago. Alternatively, protonation of the hydroperoxy-iron species on the proximal oxygen gives iron-complexed hydrogen peroxide, which can dissociate. This dissociation is reversible, and P450 enzymes can be shunted with hydrogen peroxide to give an active oxidant.

The exact mechanistic details of oxygen insertion into the C–H bond are, however, still the subject of intense discussion. Recent mechanistic studies, as reviewed [52–55], indicate that the cytochrome P450-catalyzed hydroxylation reaction is complex, involving multiple mechanisms and oxidants. In addition to the iron–oxo species, the existence of another electrophilic oxidant, either the hydroperoxo–iron species or iron-complexed hydrogen peroxide, seems apparent (Fig. 2). This other electrophilic oxidant seems to react by insertion of OH^+ into the C–H bond to give the protonated alcohol [56, 57]. It has, furthermore, been proposed that the iron–oxo species reacts through different spin states, a high-spin quartet state and a low-spin doublet state (Fig. 2) [58, 59]. The reactions via both states start in a similar manner that has the appearance of a hydrogen-abstraction reaction. After reaching the transition states for the abstraction, however, the energetics of the two pathways diverge. The reaction on the low-spin ensemble pro-

ceeds through a radical-like species that collapses with no or a low barrier to give the alcohol product; that is, the reaction is effectively an insertion. The reaction on the high-spin ensemble has a considerable barrier to collapse. Thus, this pathway gives a true radical intermediate and resembles the rebound mechanism [60, 61].

2.1.3.2.2 Nonheme Iron Oxygenases

Nonheme iron oxygenases participate in a range of reactions as broad as that found for heme-containing oxygenases but are generally much less well understood, although understanding of the biological significance and chemical properties of nonheme iron oxygenases has increased dramatically in recent years [62]. This enzyme category can be divided into two groups, mononuclear nonheme iron enzymes and binuclear nonheme iron enzymes (Fig. 1).

The former group mainly catalyzes dioxygenations and lipooxygenations, but also hydroxylations [63, 64]. As an example, pterin-dependent hydroxylases catalyze aromatic oxygenations. Here, we focus on monooxygenases catalyzing oxyfunctionalization of sp^3 -hybridized carbon atoms. Such activity can also be found among mononuclear nonheme iron oxygenases, namely in the group of α -ketoglutarate-dependent iron enzymes [65–67]. Most of these enzymes are hydroxylases and catalyze the coupled reaction of hydroxylation of an (unactivated) C–H bond in a substrate and oxidative decarboxylation of the co-substrate α -ketoglutarate, forming succinate and CO_2 . Thus, α -ketoglutarate-dependent hydroxylases are actually dioxygenases. These enzymes are present in animals, plants, and microorganisms, catalyze C–H bond oxygenations primarily in large and highly functionalized molecules, and are thus important in medicine and agriculture. Some α -ketoglutarate-dependent dioxygenases are used in the synthesis of pharmaceutical compounds.

Among the known reactions catalyzed by oxygen dependent binuclear nonheme iron enzymes, usually containing a bridged di-iron center in the active site, are hydrocarbon monooxygenations, fatty acid desaturations, and ribonucleotide reduction [63, 68]. With regard to hydrocarbon oxyfunctionalization, methane monooxygenase (MMO) is the best-studied nonheme di-iron monooxygenase.

Methane monooxygenases catalyze the NADH-dependent insertion of one atom of O_2 into the exceptionally stable C–H bond of methane to form methanol, the first step in the degradation of methane by methanotrophs such as *Methylosinus trichosporium* and *Methylococcus capsulatus*. The soluble MMOs typically have a broad substrate spectrum including saturated and unsaturated, linear, branched, and cyclic hydrocarbons up to about C_8 , and aromatic, heterocyclic, and chlorinated compounds [69, 70]. The MMO system consists of three protein components [71], a hydroxylase (MMOH) containing a carboxylate- and hydroxo-bridged di-iron cluster in the active site, a reductase (MMOR) channeling electrons from NADH to MMOH, and a small effector protein termed component B (MMOB) with several roles in MMO catalysis, including control of substrate access and enhancement of the electron transfer from MMOR to MMOH [70, 72, 73].

The first crystal structure for the hydroxylase component was reported by Rosenzweig et al. [74] for *M. capsulatus* MMOH, followed by the crystal structure

of MMOH from *M. trichosporium* OB3b [75]. Furthermore, *M. capsulatus* MMOH has successfully been crystallized in different crystal forms, oxidation states, and in the presence of various substrates and products. Together with spectroscopic studies, this enabled detailed analysis of structural changes during the catalytic cycle [70]. Four glutamate and two histidine residues coordinate the di-iron centers of MMOH. The remaining coordination sites are occupied by solvent-derived ligands. Very similar structures occur in other enzymes using a carboxylate-bridged di-iron center to activate dioxygen such as ribonucleotide reductase and soluble stearoyl-ACP Δ^9 desaturase [76–78].

Current understanding of the MMO catalytic cycle is shown in Figure 3 [68, 79–81]. The cycle starts with the NADH coupled reduction of the diferric [Fe(III)-Fe(III)] form to the diferrous [Fe(II)Fe(II)] form of MMOH involving MMOR and MMOB, the latter being bound to MMOH throughout the catalytic cycle. Oxygen seems to react in several steps with reduced MMOH to form compound P. A Michaelis complex with oxygen bound to the enzyme, but not to the dinuclear iron center, a terminal superoxo, and a bridging peroxo complex (compound P*) at the di-iron cluster have been proposed as intermediates [82–86]. Compound P has been shown by Mössbauer spectroscopy to harbor a diferric cluster [87]. Mössbauer and other spectroscopic studies of *Methylosinus trichosporium* MMOH have suggested that P is a diferric peroxy species and both the P formation and decay reactions were shown to require a proton, suggesting that P may be a hydroperoxo adduct, as shown in Fig. 3 [82]. P spontaneously converts to Q, which has been shown to react with methane to yield methanol [88]. It has been proposed that Q contains a bis- μ -oxo Fe(IV)₂ cluster in which the two single-atom oxygen bridges form a so-called “diamond core” [87]. Q is electronically equivalent to the iron–oxo intermediate thought to be one of the reactive species in cytochrome P450 (Fig. 2) [52]. After reaction of Q with the substrate via a putative intermediate R, product-bound compound T is formed, and, with release of the product, the resting diferric state of MMOH is regenerated in the rate-limiting step of the cycle [88].

There is currently significant debate about the mechanism of substrate oxidation by Q [62, 80, 81, 89]. Studies examining the MMO-catalyzed oxidation of norcarane, of which the products derived from radical and cationic rearrangements clearly differ, indicated that both radical and cationic species are involved in product formation with a radical lifetime on the order of 20–150 ps [79, 90]. There is, furthermore, evidence suggesting that compound P may be able to effect alkene epoxidation directly [91]. Thus, in analogy with P450, multiple mechanisms and oxidants may be involved in the oxygenation of different substrates by MMO.

Alkane monooxygenase (AMO) of *P. putida* GPo1 (formerly known as *P. oleovorans* GPo1 = TF4–1L = ATCC 29347 [92–94]) is another member of the family of binuclear nonheme iron enzymes. It naturally catalyzes the ω -hydroxylation of medium chain length alkanes (C₅–C₁₂) to alkanols, the first step in the degradation of alkanes [95–98]. AMO consists of an integral membrane protein, the hydroxylase component AlkB, and two soluble proteins, rubredoxin AlkG and rubredoxin reductase AlkT [99–101]. Its substrate spectrum, for which a tryptophan at position 55 was found to be critical, includes a wide range of linear, branched, and cyclic alkanes, and alkyl-

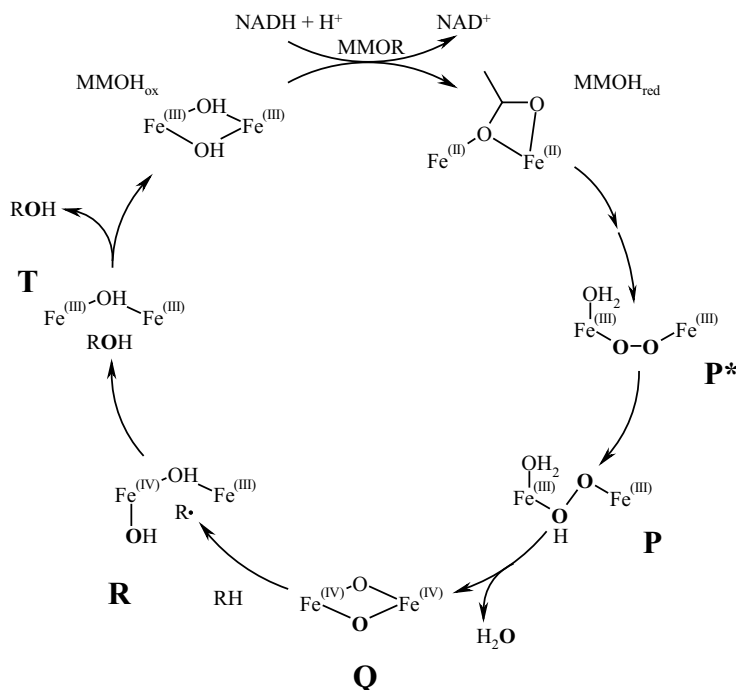


Figure 3. The catalytic cycle of soluble MMO. Oxygen atoms derived from molecular oxygen are shown in bold. Compounds P^* , P , Q , R , and T are described in the text. MMOR, reductase component of MMO; MMOH, hydroxylase component of MMO. Adapted from [68, 79].

benzenes [102, 103]. Furthermore, epoxidation of terminal alkenes, sulfoxidations, demethylations, and aldehyde formation have been reported [104–107].

Studies on the topology of AlkB indicated a structure containing six transmembrane segments [108]. In this model, the amino terminus, two hydrophilic loops, and a large carboxy terminal domain are oriented towards the cytoplasm, and three very short loops are exposed to the periplasm. Similarly to MMOH, it has been proposed that AlkB contains an active site di-iron cluster, which is oxo- or hydroxo-bridged [109, 110]. In contrast with water-soluble proteins of the di-iron-carboxylate type (for example soluble MMO), however, in which the di-iron centers are coordinated via histidines and the carboxyl groups of aspartate or glutamate, AlkB ligates the di-iron core via histidines only. Thus, AlkB was suggested to represent a new type of nonheme di-iron enzyme [111]. Sequence analyses indicated that a variety of nonheme integral membrane enzymes, including AlkB, contain a highly conserved 8-histidine motif, which was shown to be essential for catalytic activity in membrane bound rat stearoyl-CoA desaturase and suggested to provide ligands for the O_2 -activating di-iron clusters in integral membrane enzymes of this family [109, 112]. As for the examination of the mechanism of MMO-

catalyzed C–H bond oxygenation, norcarane was tested as substrate to distinguish between radical and cation intermediates in AMO catalysis. Analogous to MMO, the results indicate the intermediacy of a carbon-centered substrate radical, in this instance with a relatively long lifetime of approximately 1 ns [113]. Recent genetic experiments have suggested that enzymes with high homology to AlkB, especially in the histidine-rich region, are widely distributed in nature [34, 114–118].

Xylene monooxygenase (XMO) is another interesting example of an integral membrane nonheme di-iron enzyme containing a histidine cluster [112]. XMO initiates the degradation of toluene and xylenes in *P. putida* mt-2 by hydroxylation of a methyl side chain of the aromatic ring. Using *Escherichia coli* recombinants, XMO was shown to have a large substrate spectrum including *m*- and *p*-ethyl-, methoxy-, nitro-, and chloro-substituted toluenes, *m*-bromo-substituted toluene, and styrene, which is transformed into (*S*)-styrene oxide with an enantiomeric excess of 95% [119–121]. Furthermore, *E. coli* recombinants containing XMO were found to catalyze the multistep oxidation of xylenes to corresponding alcohols, aldehydes, and acids via individual monooxygenation reactions [122]. XMO consists of two polypeptide subunits [123, 124], the integral membrane hydroxylase XylM [125, 126] and the NADH:acceptor reductase XylA, transferring reducing equivalents from NADH to XylM [127]. XylM has 25% amino acid sequence homology with AlkB [124] and contains six membrane-spanning helices and four histidine clusters of HXX(X)(H)H, in analogy to AlkB [112, 126]. Furthermore, using the radical clock norcarane in a whole-cell assay indicated the intermediacy of a substrate radical with a lifetime of 0.2 ns [128].

Sequence analyses revealed that the class of histidine cluster containing integral membrane proteins is distributed among almost all organisms and includes many oxygen-requiring enzymes such as epoxidases, acetylenases, conjugases, ketolases, decarboxylases, methyl oxidases, desaturases, hydroxylases, and enzymes capable of both hydroxylation and desaturation [129–132]. The dual ability for hydroxylation and desaturation also was found for soluble castor stearyl-ACP Δ^9 desaturase and MMO [133, 134], underscoring the similarity of the mechanisms among nonheme di-iron enzymes of the soluble type, with di-iron clusters rich in carboxylate ligands such as MMO, and the membrane-bound type, with histidine-coordinated di-iron centers such as AMO and XMO.

2.1.3.3 Applications of Oxygenase Catalysis in Organic Syntheses

The development of oxygenase-based bioprocesses suitable for industry faces hurdles that are not experienced by biocatalytic processes involving easy-to-use enzymes such as hydrolases, isomerases, or lyases. Oxygenases are often unstable, consist of multiple components, of which some might be membrane-bound, and require costly cofactors such as NAD(P)H [135]. Such characteristics restrict the use of isolated enzymes in practical applications [136]. Despite promising progress in the application of isolated oxygenases, including enzyme immobilization and/or sophisticated cofactor regeneration systems [43, 137–141], industrial applications of oxygenases are usually based on whole-cell biocatalysis.

Requirements of industrial applications of enzymes often differ from natural enzyme properties evolved for optimum survival of a species in a specific environment. For application of oxygenases, critical intrinsic enzyme properties include catalytic rates of the order of $1\text{--}50\text{ s}^{-1}$, uncoupling, and multiple oxidation. Similarly, the microbial host, which, in whole-cell-based oxygenase catalysis, is used for enzyme production and cofactor regeneration, is not optimized to sustain high oxygenase, substrate, and product levels. Thus, physiological aspects such as product degradation, effects of (heterologous) expression and activity of oxygenases, cofactor recycling, and toxicity of substrates and products have to be considered. Application-related requirements can be addressed from the biocatalyst side, adapting the biocatalyst to the process conditions (biocatalyst engineering), and from the process side, adapting the process conditions to optimally exploit the biocatalyst (biochemical process engineering). Bioprocess engineering faces further challenges such as high oxygen requirements of the whole-cell biocatalyst and downstream processing. Below, these critical issues and strategies to overcome them are discussed on the basis of five examples.

The discovery of appropriate biocatalysts for the desired reaction is crucial for successful biocatalysis. Oxygenases initiating microbial hydrocarbon degradation usually have a broad substrate spectrum with activity toward unnatural substrates, which are not further degraded, as shown for *P. putida* GPo1 [102]. Thus, interesting biocatalysts could be identified by isolating microorganisms growing on *n*-alkanes from environmental samples [142] (Engesser K.-H., Schmid A. et al. unpublished results) and by screening them for the ability to oxyfunctionalize unnatural substrates [143]. *Sphingomonas* sp. HXN-200, a strain isolated by this approach, was found to catalyze, by means of P450 monooxygenases, the hydroxylation of various N-substituted pyrrolidines [144] (Fig. 4), pyrroline-2-ones [145], piperidin-2-ones [146], piperidines, and azetidines [147] with moderate to high regio- and enantioselectivity and at initial reaction rates between 2 and 29 U (g cdw)^{-1} ($\mu\text{mol per minute per gram of cell dry weight}$). Strain HXN-200 was routinely produced by batch fermentation, stored at -80°C , and thawed for use at 30°C . The highest productivity was achieved with growing cells [144].

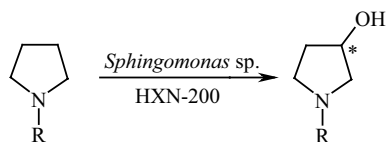


Figure 4. Hydroxylation of N-substituted pyrrolidines by *Sphingomonas* sp. HXN-200. *Indicates the introduction of a chiral center. R = CH_2Ph , COPh , $\text{CO}_2\text{CH}_2\text{Ph}$, CO_2Ph , $\text{CO}_2\text{t-Bu}$.

The “docking/protecting” group concept is another approach to achieve selective C–H oxyfunctionalization of otherwise inert compounds, avoid side reactions, and/or improve regio- and stereoselectivity and activity [148, 149]. A substrate is modified by introducing a “docking/protecting” group, which can be removed

after the reaction. This concept enabled the successful hydroxylation of unactivated C–H bonds in substrates containing carboxylic acid [148, 150], ketone [148, 151, 152], alcohol [148, 153], amine [144, 147, 154], lactam [145, 146], and aldehyde [153] functionality. Figure 5a shows the “protection” of the acid group of cyclopentanecarboxylic acid yielding the corresponding benzoxazole followed by biohydroxylation with *Cunninghamella blakesleeana* DSM 1906 [150]. The use of a chiral auxiliary to modify 4-methyl-2-pentanone enabled hydroxylation with a diastereoselectivity as high as 99% (Fig. 5b) [152].

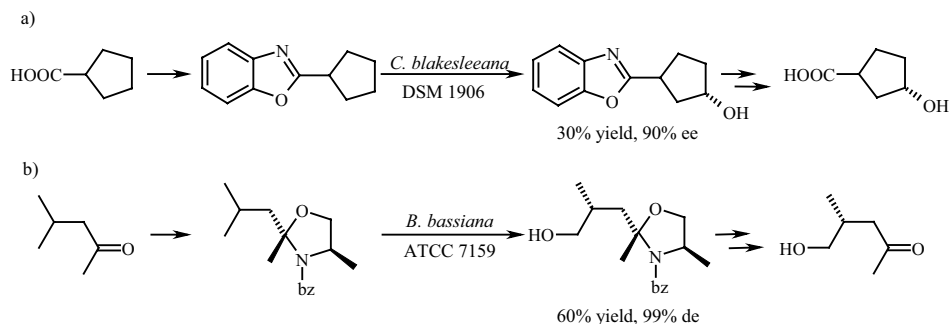


Figure 5. Stereospecific hydroxylation of cyclopentane carboxylic acid (a) and 4-methyl-2-pentanone (b) by two fungus species using the “docking/protecting” group concept.

The whole-cell biooxidation of natural substrates such as *n*-alkanes necessitates the use of genetically engineered biocatalysts instead of wildtype strains, to avoid product degradation (Fig. 6). The gene of interest can, for example, be introduced into a heterologous host (yielding a recombinant strain), or the gene(s) encoding product-degrading enzyme(s) can be knocked out (yielding a knockout strain). Both strategies were combined to construct *P. putida* PpS8141 harboring alkane monooxygenase (AMO), which was used for production of primary alkanols from alkanes in a two-liquid phase system consisting of an aqueous medium and a bulk alkane phase [155].

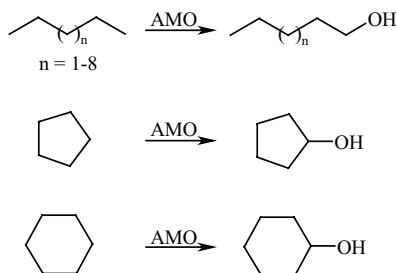


Figure 6. Hydroxylation of alkanes catalyzed by recombinant microbes harboring the alkane monooxygenase (AMO) of *P. putida* GPo1 (formerly known as *P. oleovorans* GPo1). A fraction of the broad substrate spectrum of AMO is shown [102].

With cells growing on pyruvate to cell concentrations of approximately $1 \text{ (g cdw)} L_{\text{aq}}^{-1}$, a maximum specific activity of $60 \text{ U (g cdw)}^{-1}$ and a mean volumetric productivity of $0.088 \text{ g } L_{\text{aq}}^{-1} \text{ h}^{-1}$ were achieved. For production of octanoate from octane in a similar system, cells growing to a concentration of $38 \text{ (g cdw)} L_{\text{aq}}^{-1}$ enabled a productivity of $1.33 \text{ g } L_{\text{aq}}^{-1} \text{ h}^{-1}$ [156]. The use of growing cells with high metabolic activity is thought to guarantee the maintenance of high oxygenase levels and NAD(P)H regeneration rates. During cell growth, however, a variety of reactions, especially oxidative phosphorylation, also consume reduction equivalents [157]. The presence of an active NAD(P)H-consuming oxygenase will thus have an impact on cell metabolism, reduce growth yields on energy sources, cause stress, and reduce growth rate, viability, and metabolic activity [122, 155, 158–160]. Further investigations are required to elucidate if and to what extent cofactor recycling is limiting in whole-cell biooxidations. On the basis of this research, bioprocess engineering to optimally exploit cell metabolism, metabolic engineering, and the introduction of an additional cofactor regeneration activity may help to maximize in-vivo oxygenation rates.

Metabolic engineering can also be used to overproduce cell metabolites, which serve as substrate for an oxygenase. *trans*-4-Hydroxy-L-proline has been produced both from L-proline and directly from glucose (Fig. 7). For hydroxylation of L-proline, a proline 4-hydroxylase gene from *Dactylosporangium* sp. RH1 was expressed in *E. coli*, the codon usage of the 5' end of the gene was optimized, and the recombinant *E. coli* was cultivated in a medium containing L-proline and glucose [161]. The cosubstrate of proline 4-hydroxylase, α -ketoglutarate, was efficiently supplied from glucose via cell metabolism. The production of *trans*-4-hydroxy-L-proline from glucose was achieved by introducing additional copies of two genes involved in L-proline synthesis in *E. coli* – a mutated *proB* gene encoding a γ -glutamyl kinase, which is resistant to feedback inhibition by L-proline, and the *proA* gene encoding glutamate semialdehyde dehydrogenase [162]. Furthermore, the *E. coli* host contained a *putA* mutation, which rendered the strain unable to degrade L-proline.

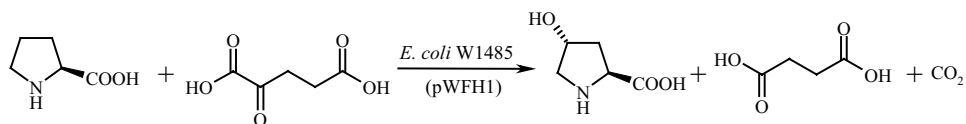


Figure 7. Hydroxylation of L-proline to *trans*-4-hydroxy-L-proline by proline 4-hydroxylase. The cosubstrate α -ketoglutarate is continuously supplied by the metabolism of growing *E. coli* W1485 (pWFH1), which served as biocatalyst.

Most potentially interesting substrates and products of oxygenases are poorly water-soluble and/or toxic to living cells [31, 33, 163–166]. Organic–aqueous two-liquid-phase systems are a valuable biotechnological tool for biotransformation of apolar compounds [14, 167–170]. The concept enables use of high overall concentrations of toxic apolar chemicals within the two-liquid phase system, by regulat-

ing substrate and product concentrations in the aqueous biocatalyst microenvironment, and simple product recovery [171–173]. Furthermore, the partitioning behavior of substrate and product can be exploited to avoid kinetic product inhibition, to guide equilibrium reactions in a desired direction, to enhance the enantiomeric excess, and to control multistep reactions [159, 166, 174–177]. The two-liquid-phase concept enabled, for example, prevention of substrate and product toxicity during the allylic hydroxylation of limonene to perillyl alcohol catalyzed by recombinant *P. putida* GPo12 harboring a cytochrome P450 alkane hydroxylase from *Mycobacterium* sp. strain HXN-1500 (Fig. 8) [178].

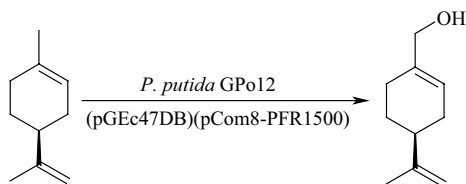


Figure 8. Hydroxylation of L-limonene to (–)-perillyl alcohol by cytochrome P450. Growing cells of *P. putida* GPo12 (pGEc47ΔB)(pCom8-PFR1500) containing the P450 alkane monooxygenase of *Mycobacterium* sp. strain HXN-1500 are used as catalyst.

Recombinant expression in a *Pseudomonas* host was chosen, because the wild-type strain was difficult to cultivate and is considered a biosafety class II organism, and because *Pseudomonas*, unlike *E. coli*, is known to express P450 enzymes at high levels. Although a heterologous inducible expression system was used, P450 enzyme expression could only be induced during growth on alkanes. Other growth substrates, for example citrate, did not enable proper induction. Co-metabolism in a two-liquid-phase system enabled a specific activity of 3 U (g cdw)^{–1} and the production of gram amounts of perillyl alcohol.

2.1.3.4 General Conclusion and Outlook

Biocatalysis has been developed as a key technology in organic synthesis [15, 179, 180]. It is ideally suited to catalyzing demanding reactions, for example selective functionalization of nonactivated carbon atoms. Future research is expected to result in faster screening and design procedures for catalysts, higher turnover rates and total turnover numbers, robust methods based on isolated enzymes and nongrowing cells, and a better understanding of catalyst function on the molecular and process levels.

Experimental

The successful application of (living) microbial cells as catalysts for C–H bond oxyfunctionalization depends on the correct handling of the biological reagent. Meth-

ods and techniques covering such aspects as catalyst screening, catalyst characterization, reaction engineering, enzyme/whole cell engineering, induction of gene expression, product recovery, and process economics are available in the specialized biocatalysis literature [136, 181–188]. A comprehensive introduction to aspects of handling of wild type (not genetically engineered) microbes for selective oxyfunctionalization of saturated carbon atoms using basic microbiological and biochemical infrastructure was given by Azerad [189]. As discussed above, high turnover rates of the cellular catalysts are frequently found for growing cells. Cell growth is best achieved in monoseptic, stirred tank bioreactors under batch or fed-batch conditions, preferably in defined minimum cultivation media [190]. In an application of recombinant microbes as catalysts, national security guidelines for the handling of genetically engineered organisms must be taken into account.

Many potential substrates and/or inducers of gene expression for oxygenase catalysis are volatile and flammable. Because whole-cell biocatalysts performing oxygenation reactions require oxygen for the biotransformation and for endogenous respiration, high oxygen input rates are essential. The danger of explosion can essentially be overcome by the addition of inert carrier solvents such as hexadecane and bis(2-ethylhexyl)phthalate. In such systems, substrates and/or inducers can be added up to a volume fraction of 30% (v/v) of the organic phase without explosion hazard [160, 170, 191]. In addition, substrate concentrations can be maintained at a level below 30% (v/v) by a tailored and controlled feeding regime. To address safety issues and to improve the performance of aerobic bacterial bioprocesses involving flammable organic solvents, Schmid et al. and Bioengineering AG (Wald, Switzerland) have developed a high-pressure explosion-proof bioreactor [192]. Oxygen input into production scale bioreactors at high rates remains a big challenge, however. Based on air as oxygen source, an upper limit for oxygenase activity in living cells of 500 U L^{-1} aqueous medium, corresponding to a productivity of $3 \text{ g L}^{-1} \text{ h}^{-1}$ for a 100 g mol^{-1} product, was estimated for standard industrial scale reactors [33]. This estimate included endogenous respiration of $10 \text{ g cells L}^{-1}$ and assumed an oxygen transfer coefficient ($k_L a$) of 200 h^{-1} . Improving the specific activity of whole-cell biocatalysts and thus reducing the cell concentration was considered to reduce the relative amount of oxygen required for respiration, which increases the upper limit for volumetric oxygenase activity. On the other hand, higher oxygen input rates may be achieved by technical solutions and by aeration with oxygen-enriched air, if economically and technically feasible.

2.1.4

Transition Metal-catalyzed Oxidation of Alkanes

Gaurav Bhalla, Oleg Mironov, Cj Jones, William J. Tenn III, Satoshi Nakamura and Roy A. Periana

2.1.4.1 Introduction

The development of new, selective, energy-efficient chemistry for the direct, oxidative conversion of alkanes at temperatures below 250°C is one of the most challenging and potentially important problems in contemporary catalytic science

today [1, 2g]. Success in this field could lead to new energy and petrochemical technologies in the 21st century that is environmentally, economically superior and enable vast reserves of underutilized natural gas to be economically employed as feed stocks for fuels and chemicals. The direct, catalytic, oxidative conversion of alkanes at low temperatures to products such as versatile alcohols presents many challenges. However, suitably designed homogenous complexes have been identified that can coordinate to and cleave the C–H bond of alkanes at low temperatures with extraordinary selectivity via the C–H activation reaction [2]. This reaction is of particular interest both scientifically and economically, because it could be used to design the next generation of low-temperature, selective, hydrocarbon oxidation catalysts based on the generalized catalytic sequence shown in Fig. 1. Despite the large amount of work performed on the C–H activation reaction over the last three decades, however, there have been relatively few reports of catalytic systems based on this approach that enable direct conversion of alkanes to useful products such as alcohols or other oxygenated products. This is probably because of challenges associated with designing complexes that (1) react by the C–H activation reaction, (2) generate functionalized products in a catalytic sequence, and (3) are also stable to the oxidizing conditions required for the oxidative functionalization reaction.

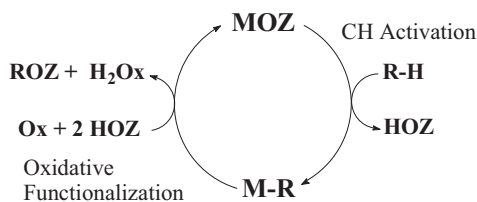


Figure 1. Catalytic scheme for alkane oxy-functionalization based on the C–H activation reaction.

In this review homogeneous complexes that catalyze the oxidative conversion of alkanes to products containing C–O bonds and which may operate via the C–H activation reaction are discussed, with emphasis on our own research. Some notable systems that catalyze this transformation are shown in Fig. 2.

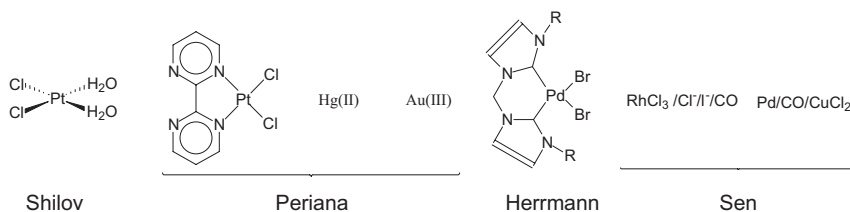


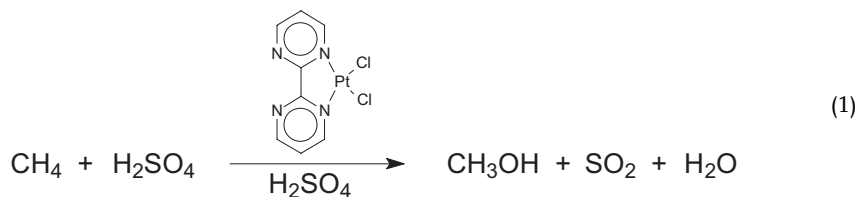
Figure 2. Examples of systems that oxidatively convert alkanes to C–O functionalized products.

Most organic chemistry characterized by mild reaction conditions and high reaction selectivity can be classified as inner-sphere coordination chemistry at car-

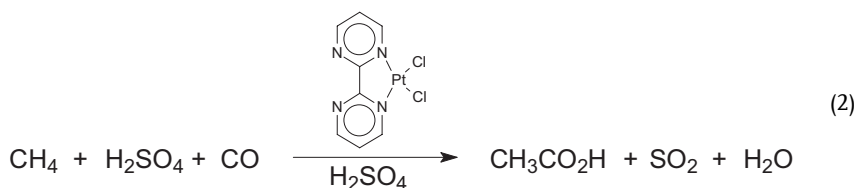
bon centers, i.e. chemistry that occurs within the first-coordination sphere of three, four, and five-coordinate carbon species. Although the coordination chemistry of carbon in functionalized organic molecules is well-developed, the coordination chemistry of alkanes is much less so and is usually only possible with very reactive species such as super acids, super bases, free-radicals, or carbenes. These very reactive species are generated either under high-energy conditions or with high-energy precursors and are usually not amenable to efficient syntheses with alkanes. In this review, we classify the C–H activation reaction as a coordination reaction of alkanes with a reactive species, “MOZ”, that occurs within the inner-sphere of the carbon to generate an M–C intermediate, Fig. 1, without the involvement of high-energy species such as free-radicals, carbocations, or carbanions. An important consequence of the coordination characteristics of the C–H activation reaction are low activation barriers and remarkable selectivity. Thus, the C–H activation reaction of alkanes has been reported below room temperature and with greater selectivity for primary over tertiary C–H bonds, arene C–H over alkane C–H bonds, and reactions of alkanes over alcohols [2]. The high rate of the C–H activation reaction results partly from formation of strong M–C bonds that compensate for the cleavage of the strong C–H bonds (thermodynamics) and the availability of appropriate orbitals on the central atom, M, that ensure good overlap in the transition states (kinetics). Coupled with the possibility of oxidative functionalization of the M–C intermediate to functionalized products with regeneration of “MOZ”, the C–H activation reaction can provide a basis for the development of the next generation catalysts for the atom-efficient and energy-efficient conversion of alkanes directly to useful products.

2.1.4.2 C–H activation and Functionalization by Pt(II)

During the 1970s Shilov published extensively on the reactions of alkanes in aqueous solutions of platinum(II) complexes [3]. The reactions are typically carried out in aqueous hydrochloric acid as solvent at <100 °C with chloride salts of Pt(II) as catalyst and the chloride salts of Pt(IV) as the stoichiometric oxidant. Typical reaction yields, based on added methane, are less than 3 % with >75 % selectivity to methanol and methyl chloride. It was proposed the reaction proceeded via C–H activation to generate alkyl platinum intermediates in reactions with alkanes and later results are consistent with this proposal [4]. This system is one of the first systems proposed to operate via the C–H activation reaction and to generate potentially useful functionalized products. The key disadvantages of the Shilov system were the low rates (catalyst turn-over-frequency, TOF, <10^{−5} s^{−1}), short catalyst life (turn-over-number, TON, <20), and the use of Pt (IV) as a stoichiometric oxidant.

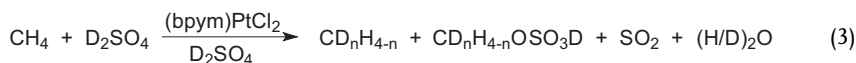


One advantage of the use of transition metals for the C–H activation reaction is that, as a result of the multiple available coordination sites, spectator ligands can be used to mediate the chemistry of the metal center. By using ligands and alternative oxidants with Pt(II) we developed a very efficient catalyst for oxidation of methane to methanol based on the C–H activation reaction. This system, dichloro(κ^2 -{2,2'-bipyrimidyl})platinum(II), Pt(bpym)Cl₂, is stable and active for the conversion of methane to methanol in concentrated sulfuric acid (Eq. 1) with yields of over 70 % methanol (based on added methane), selectivity >90 %, and catalyst TOF of $\sim 10^{-3} \text{ s}^{-1}$ at 300 psig methane [5]. The Pt(bpym)Cl₂ complex is stable in hot concentrated sulfuric acid for weeks and catalyst TON of >300 have been observed without decomposition. The key issues with this system for alkane oxidation are the slow rates (TOF $\sim 1 \text{ s}^{-1}$ are desirable) and the inhibition of the catalyst by water and methanol that limit concentration of products to $\sim 1.5 \text{ M}$. It has been estimated that at concentrations below $\sim 3 \text{ M}$, the cost of separation of the products from sulfuric acid is not economical. The catalyst system is applicable to higher alkanes, and reactions with ethane lead predominantly to the generation of ethylene glycol. Reactions with higher alkanes are less selective but oxygenated products can be obtained. We have been examining the possibility of using this stable, active system to generate acetic acid by use of the oxidative carbonylation reaction shown in Eq. (2). Initial studies indicate that in the presence of low levels of CO, the oxidation of methane with the Pt(bpym)Cl₂/H₂SO₄ system can be selectively diverted to generate acetic acid instead of methanol [6].



Experimental and theoretical studies are consistent with the Pt(bpym)Cl₂ system proceeding via the electrophilic substitution (ES) C–H activation reaction mechanism shown in Fig. 3 [7]. This is probably because of the increased electrophilicity of the metal on protonation of the bpym ligand. Consistent with the proposed formation of a Pt–CH₃ intermediate, when the reactions are carried out in D₂SO₄, multiple deuterium incorporation occurs into both methane and methyl products, Eq. (3). As further evidence for the intermediacy of a Pt–CH₃ species, treatment of independently synthesized (bpym)Pt(CH₃)(CF₃CO₂) with D₂SO₄ at 150 °C also leads to the generation of deuterated methane and methanol when Pt(IV) (as H₂Pt(OH)₆) is present as an oxidant. In catalytic reactions between D₂SO₄ and CH₄ with Pt(bpym)Cl₂ at lower temperatures, $\sim 150^\circ\text{C}$, no significant amounts of oxidation products (methanol or esters) are observed after a 30-min reaction period. Under these conditions, however, extensive H/D exchange occurs between CH₄ and D₂SO₄, suggesting that C–H activation could be faster than the oxidation step, and/or functionalization step shown in Fig. 3. The relative rates of the functionalization and oxidation steps were examined by addition of

$\text{H}_2\text{Pt}^{\text{IV}}(\text{OH})_6$ as a stoichiometric oxidant to the catalytic reaction system at 150°C . In this case, in addition to deuterated methane, methanol is also formed in quantitative yield relative to the added Pt(IV). This suggests that the functionalization step is faster than the oxidation step and leads to the proposal that (above 90 % sulfuric acid) the latter is the rate-limiting step. Below this concentration of acid solvent, studies suggest that the C–H activation step is the rate-limiting step.



Experimental and theoretical studies show that the high stability of $\text{Pt}(\text{bpym})\text{Cl}_2$ complex is probably because of the unique structure and composition of the bpym ligand [7]. These studies show that the bpym ligand is protonated in strongly acidic media and that this prevents decomposition from irreversible formation of insoluble $(\text{PtCl}_2)_n$ or Pt black formation. The presence of the two nitrogen atoms in the same aromatic ring in the bipyrimidine ligand, with the chelate structure, enables electronic communication between the N-centers and prevents loss of the ligand that could result from exhaustive protonation of all the nitrogen atoms. Consistent with this proposal, although $(\text{PtCl}_2)_n$ and Pt black are both insoluble in hot sulfuric acid, addition of one equivalent of bipyrimidine ligand leads to dissolution and generation of an active, stable catalyst. Significantly, this dissolution is not observed with simpler ligands such as bipyridine.

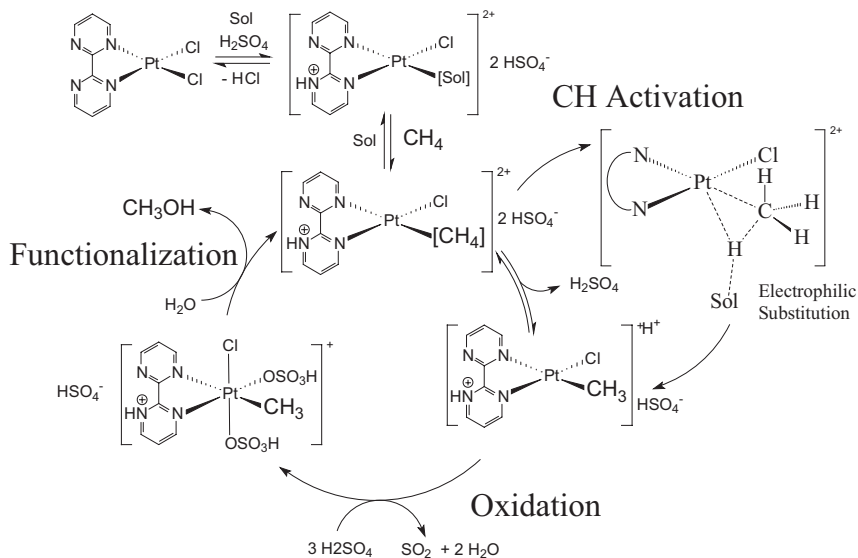
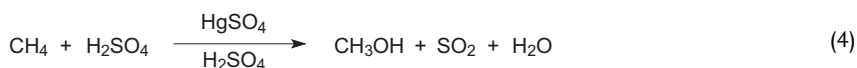


Figure 3. Proposed mechanism for methane oxidation by the $\text{Pt}(\text{bpym})\text{Cl}_2/\text{H}_2\text{SO}_4$ system.

2.1.4.3 Electrophilic C–H activation by Hg

Another strategy for developing active and stable oxidation catalysts that operate via the alkane C–H activation reaction is to use metals that can be readily dis-

solved with suitable oxidants to generate “soft”, electrophilic, oxidizing metal cations in poorly coordinating solvents. Reasoning that “soft”, electrophilic, oxidizing, third or second row metal cations, MOZ, could form relatively stable covalent bonds with methyl groups and M-CH₃ intermediates that can subsequently be oxidized, we developed the use of soluble Hg(II) cations in sulfuric acid as an effective catalyst for selective oxidation of methane to methanol [8]. Thus, reaction of methane (500 psig) with 96 % sulfuric acid at ~180 °C containing 20 mM Hg(HSO₄)₂ efficiently generates methanol at concentrations of ~1 M with selectivity >90 % and yields of ~40 % based on added methane, Eq. (4). The reaction can be carried out in triflic acid to generate the methyl triflate, but in this case the reaction is stoichiometric in Hg(II) which serves as both the catalyst and stoichiometric oxidant. This chemistry is less applicable to the higher alkanes than the Pt(bpy)Cl₂ system and although reactivity is observed, the reactions are not selective.



As shown in Fig. 4, the proposed mechanism of the Hg(II)/H₂SO₄ system is characterized by the same three steps as the Pt(bpy)Cl₂ system; C–H activation of methane, functionalization of the CH₃–Hg to generate methanol, and oxidation of the resulting Hg(I) species [8]. This system seems to be the simplest example of C–H activation of methane by an ES pathway. It is proposed that a soft, labile, powerful electrophilic species, [XHg–Sol]⁺, is generated on dissolution of HgX₂ salts in hot sulfuric acid (where Sol is H₂SO₄) that readily coordinates to and reacts with methane. Theoretical calculations show that [XHg–Sol]⁺ reacts with methane with ~29 kcal mol^{–1} barrier via a transition state in which methane is coordinated to a two-coordinate, cationic mercury species, [XHgCH₄]⁺, that loses a proton to the sulfuric acid solvent to generate CH₃HgX (Fig. 4) [9]. It seems likely that the high solvation energy of the proton in sulfuric acid and the formation of the strong [Hg–CH₃]⁺ bond are the driving forces of this step.

The proposed intermediacy of the CH₃HgX species in this step is strengthened by its direct observation in the reaction media [8, 10]. It is also found that approximately the same catalytic activity (TOF) is obtained by use of CH₃HgX directly in place of HgSO₄. Additionally, under the reaction conditions, independently synthesized CH₃HgX is readily converted to methane, methanol, and the reduced Hg₂(II) species (Hg₂X₂). It is interesting to speculate on how the methanol is formed in this reaction with CH₃HgX. Kinetic studies show that the rate of formation of CH₃OH is independent of the concentration of added Hg(II). This rules out a free Hg(II)-assisted bimolecular electrophilic substitution pathway as shown in Fig. 5. It is also well known that Hg(II) with strong field ligands such as CH₃– adopts a linear, two coordinate geometry. This would suggest that a concerted reductive elimination is unlikely. On the basis of preliminary theoretical and experimental studies we propose that the reaction occurs by solvent-assisted heterolysis of the [CH₃–Hg]⁺ species with simultaneous capture of the departing incipient fragment, CH₃⁺, by H₂SO₄ (or by either HSO₄[–] or H₂O) to generate

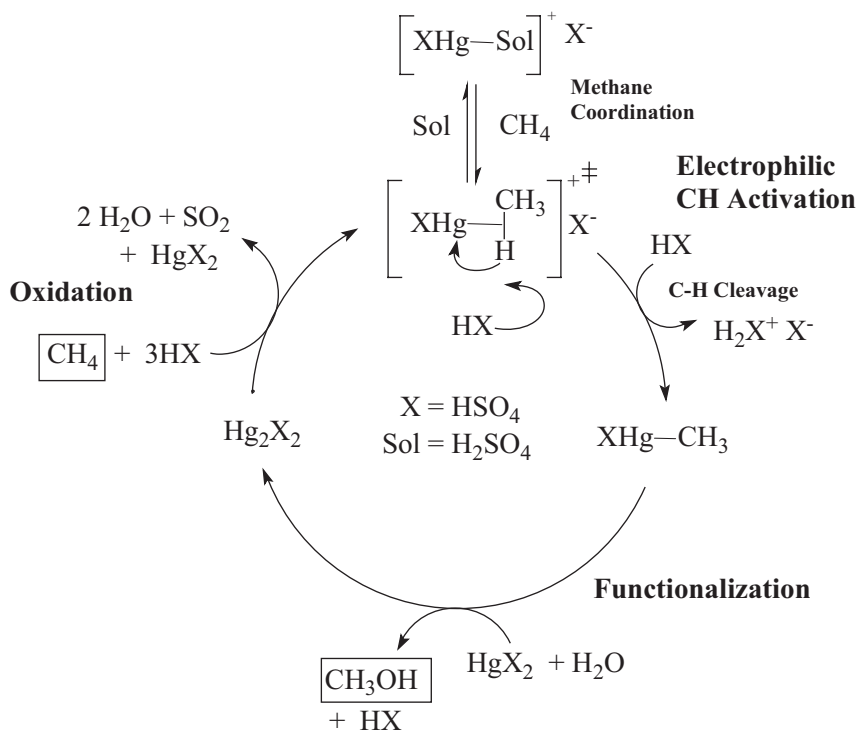


Figure 4. Proposed mechanism for methane oxidation by the Hg(II)/H₂SO₄ system.

CH₃OSO₃H, or CH₃OH and Hg(0). The Hg(0) is not observed because Hg(II) is known to react rapidly with Hg(0) to generate Hg₂(II), which is observed. Kinetic studies on [CH₃HgX] in sulfuric acid show that the activation energy of the functionalization step is higher than that for the C–H activation step. The Hg₂(II) species generated in the functionalization step has been shown to reoxidize to Hg(II) in hot sulfuric acid. Preliminary data obtained from ¹⁹⁹Hg NMR studies of the catalytic system indicate that Hg₂(II) is the resting state of the catalyst and suggests that the oxidation step is rate-determining in the overall catalytic cycle. It should be noted that the possibility of a free-radical pathway operating concurrently has been suggested by other researchers [11]. On the basis of the observation of high yields and selectivity, and that added oxygen does not change the reaction rates or selectivity, we do not believe that free-radical pathways play a significant role in this system.

The basis of the high selectivity in this system, confirmed by both theoretical and experimental results, is that the active catalyst [XHg]⁺ reacts at least 1000 times faster with the C–H bonds of methane than with those of CH₃OH, which exists primarily as the protonated, or sulfated forms, [CH₃OH₂]⁺ or CH₃O–SO₃H, respectively, in sulfuric acid. This greater reactivity of the methane C–H bonds compared with those of methanol can be traced to substantially lower reac-

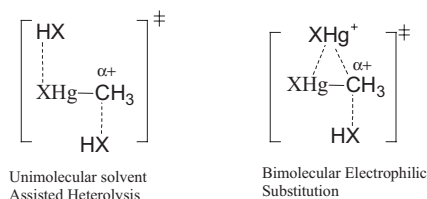


Figure 5. Possible transition states for generation of methanol from CH_3HgX , $\text{X} = \text{HSO}_4^-$.

tivity of the electrophilic $[\text{XHg-Sol}]^+$ catalyst toward the C–H bonds of methanol which, because of the electron-withdrawing effect of protonation or sulfation by H_2SO_4 (to generate $\text{CH}_3\text{OSO}_3\text{H}$), are substantially less electron-rich than those of methane.

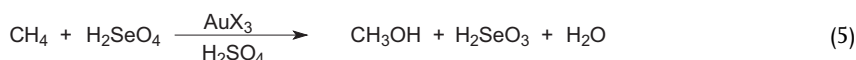
The properties of Hg(II) that lead to this efficient reaction with methane in strongly acidic media can be described as “soft”, “redox active”, and “electrophilic”. These properties are also shared by the late third and second-row elements of the periodic table, because of their high Z_{eff} , high principal quantum number, and large size. Consistently, we have found that the cations Au(III) or Au(I) [12], Tl(III) [5], I_2^+ [13], and Pd(II) [5, 6] all react readily with methane in strongly acid media to generate methanol, presumably via an ES C–H activation reaction mechanism. Consistent with the important electrophilic properties, all of these systems are inhibited by good ligands such as water or methanol or anions such as HSO_4^- or Cl^- .

2.1.4.4 Electrophilic C–H Activation by Au

Gold is unique in that in most catalytic systems based on “soft”, redox cations, only one oxidation state of the redox pair is typically active for C–H activation. As shown in the conceptual catalytic cycle shown in Fig. 6, however, both Au^{I} and Au^{III} oxidation states can be active for C–H activation and oxidative functionalization because Au^{I} (d^{10} , two-coordinate) and Au^{III} (d^8 , square planar) are isoelectronic and isostructural with the neighboring cations, Hg^{II} and Pt^{II} , respectively, both of which are known active catalysts. Consistently, Au^{III} , formed by dissolution of Au_2O_3 in sulfuric acid [14], selectively oxidizes methane to methanol with concurrent production of gold metal. Because sulfuric acid is incapable of oxidizing and dissolving gold metal the reaction is stoichiometric in Au(III) . These observations emphasized two key issues which must be addressed in developing a catalytic system based on electrophilic Au cations: (1) a system must be chosen that can maintain the Au in a soluble, cationic state, and (2) the system must not contain ligands that can coordinate to and inhibit methane coordination to the electrophilic cationic Au center. We discovered that selenic acid/sulfuric acid mixtures meet these requirements. Thus, selenic acid (H_2SeO_4) is almost as acidic as sulfuric acid [15, 16], and consequently we considered that neither the acid nor the conjugate base, HSeO_4^- , should inhibit catalysis by blocking coordination of methane

to the metal center. Equally importantly, Se^{VI} is a more powerful oxidizing agent than S^{VI} ($E^\circ = 1.5 \text{ V } \text{SeO}_4^{2-}/\text{H}_2\text{SeO}_3$; $E^\circ = 0.17 \text{ V } \text{SO}_4^{2-}/\text{H}_2\text{SO}_3$) and, selenic acid is known to oxidize gold metal [16].

We have now found that solutions of selenic acid in 96 % sulfuric acid containing Au metal can efficiently oxidize methane to methanol according to the stoichiometry shown in Eq. (5). This system is quite efficient and at 180°C with $\sim 25 \text{ mM}$ Au and 400 psig methane, methanol concentrations of 350 mM can be obtained with selectivity of 80–95 % and $\sim 10\%$ yields, based on added methane [12]. With added SO_3 (increasing the effective acid concentration) product concentrations of 650 mM, selectivity in excess of 90 %, methane conversions of $\sim 28\%$ and methanol yields of $\sim 25\%$, based on added methane, are observed. By performing the stoichiometric oxidation of methane to methanol with Au^{III} from 100°C to 200°C the overall activation barrier was estimated to be $\sim 30 \text{ kcal mol}^{-1}$.



The reaction requires dissolution of Au metal, because no reaction occurs in the absence of selenic acid when the reaction is conducted with colloidal Au metal in concentrated sulfuric acid as solvent. Consistently, control reactions show that Au metal is readily dissolved by 3 M selenic acid in 96 % sulfuric acid as solvent at temperatures below 180°C .

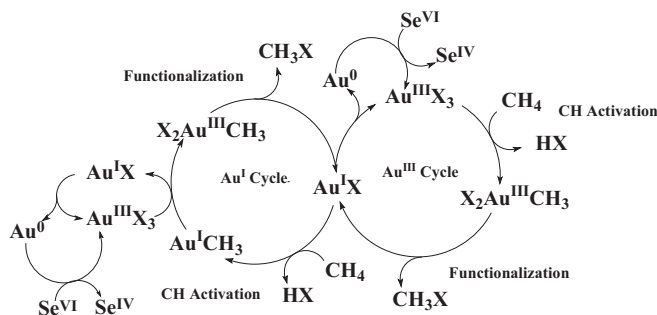


Figure 6. Proposed catalytic cycles for methane oxidation with the $\text{Au}(\text{I})/(\text{III})/\text{H}_2\text{SeO}_4/\text{H}_2\text{SO}_4$ system.

Theoretical calculations suggest that the C–H activation steps are rate determining in both cycles [12]. Consistent with the requirement for strongly acidic solvent for reaction, calculations show the $\text{Au}(\text{III})$ cation operates via an ES C–H methane activation reaction with a barrier of $\sim 28.1 \text{ kcal mol}^{-1}$. In the Au^{I} cycle, an oxidative addition (OA) or “insertion” C–H activation reaction mechanism is found to be favored and is $\sim 7.0 \text{ kcal mol}^{-1}$ lower in energy than the ES C–H activation pathway for Au^{III} . These energetics do not take into account the relative concentrations of the Au^{III} and Au^{I} cations in solution, however. The concentration of Au^{I} should be significantly lower than that of Au^{III} in the presence of excess oxidant, Se^{VI} . A difference of $7.0 \text{ kcal mol}^{-1}$ corresponds to ratio of $\sim 2500:1$ at 175°C , and thus if the

ratio of Au^{I} to Au^{III} is less than 1:2500, the Au^{III} pathway would be favored. Because this is a feasible ratio given the strong oxidizing properties of Se(VI) , both the Au^{I} and Au^{III} cycles shown in Fig. 6 are possible. Description of the C–H activation reaction with Au(I) as an oxidative addition (OA) mechanism would seem to imply that the Au(I) is an electron-rich metal center. Because Au(I) is also expected to be a good “electrophile” and is known to be a powerful oxidant, however, this suggests that the use of the OA terminology to describe this C–H activation reaction is less accurate than describing the reaction as an electrophilic “insertion” mechanism. The oxidative functionalization step is found to be viable with a $\text{Au}^{\text{III}}\text{--CH}_3$ intermediate and proceeds with a low barrier ($10.7 \text{ kcal mol}^{-1}$) via an $\text{S}_{\text{N}}2$ type attack on the methyl group by a free bisulfate ion, as was found for reaction of the $\text{Hg}^{\text{II}}\text{--CH}_3$ and $\text{Pt}^{\text{IV}}\text{--CH}_3$ intermediates.

2.1.4.5 Oxidative Carbonylation of C–H bonds by Pd(II)

After Pt(II) , Pd(II) is the other system most examined for oxidation of alkanes. Thus, Sen reported that $\text{Pd}(\text{CF}_3\text{CO}_2)_2$ in $\text{CF}_3\text{CO}_2\text{H}$ will react stoichiometrically with methane to generate the corresponding methyl esters. Here Pd(II) plays the role of catalyst and oxidant [17]. In later developments it was shown the use of $\text{Cu(II)}/\text{O}_2/\text{CO}$ with Pd black on carbon in $\text{CF}_3\text{CO}_2\text{H}$ at 85°C enabled the catalytic conversion of methane to the methyl ester in $\sim 2\%$ yield based on added methane, with high selectivity, a calculated TOF of 0.02 s^{-1} , and TON >3000 [17]. The CO in this system is a sacrificial reductant and is consumed in reactions with O_2 , presumably to generate the active catalyst. The use of co-reductants such as CO could be expected to generate reactive peroxo species that could initiate free-radical reactions that would be characteristic of the high reactivity observed at the relatively low temperatures ($\sim 85^\circ\text{C}$). However, studies by Sen suggest that free radicals are not involved in this Pd catalyzed reaction. Sen has also shown that Rh salts in a complex system containing CO in heptafluorobutyric acid oxidize methane to both methanol and acetic acid. The oxidation of methane to methanol, ethanol, and acetic acid with this Rh system has also been reported. Recently, Herrmann reported a related bis-carbene Pd(II) -based system that oxidized methane to the ester in $\text{CF}_3\text{CO}_2\text{H}$ at 80°C using persulfate ($\text{K}_2\text{S}_2\text{O}_8$) as the stoichiometric oxidant [18]. Yields of the methyl ester of $\sim 4\%$ based on added methane (assuming $>90\%$ selectivity) and TOF of 0.06 s^{-1} were calculated from a reported TON of 30.

It will be interesting to determine if all or some of these Pd(II) systems operate via a C–H activation mechanism involving the formation of Pd-CH_3 intermediates. As far as we are aware there is no compelling evidence for Pd(II) systems operating via a C–H activation reaction mechanism involving coordination of methane and concerted C–H cleavage to generate Pd-CH_3 intermediates. Given the expected similarity between Pd(II) and Pt(II) this could be expected. One test we have used to determine if reactions involve free-radicals is to examine changes in the reaction rate and selectivity in the presence and absence of added oxygen gas. Because oxygen is thermally stable in strongly acidic media and is a well-known radical trap, it is expected that oxygen should participate if free-radicals are

involved and changes in reaction rate and selectivity could be expected. Application of this test to the Hg(II), Au(III), and Pt(bpy)₂Cl₂ systems in H₂SO₄ show that oxygen is an inert diluent and does not affect reaction rates or selectivity. We have not examined the Herrmann system, but the Sen Pd(II) systems *require* oxygen for reaction to proceed.

Pd(II) will react with methane in sulfuric acid to generate methanol with low efficiency [5]. In addition to methanol, however, we recently reported that the PdSO₄/H₂SO₄ system will efficiently catalyze the oxidative condensation of two methane molecules to generate acetic acid as shown in Eq. (6) [6]. There have been reports of the use of Pd(II) to catalyze the coupling of methane with CO [19], CO₂ [20], or carboxylic acids [21] to generate acetic acid. However, what is interesting about the PdSO₄/H₂SO₄ system for the oxidative condensation of methane to acetic acid is that this reaction proceeds *without the need for added CO or other carbon sources*. Labeling studies employing ¹³CH₄ show that ¹³CH₃¹³CO₂H is the major product and unambiguously show that both carbons of acetic acid are derived from the added methane in this one-pot reaction. This is intriguing because this is formally an eight-electron process as shown in Eq. (7) and clearly cannot proceed via one-step.



The reaction is reasonably efficient and ~12% yield of acetic acid based on added methane with a selectivity of ~90% to acetic acid can be obtained. The reaction stops after ~20 turnovers, presumably because of catalyst deactivation and the formation of Pd(0). Product formation versus time is shown in Fig. 7.

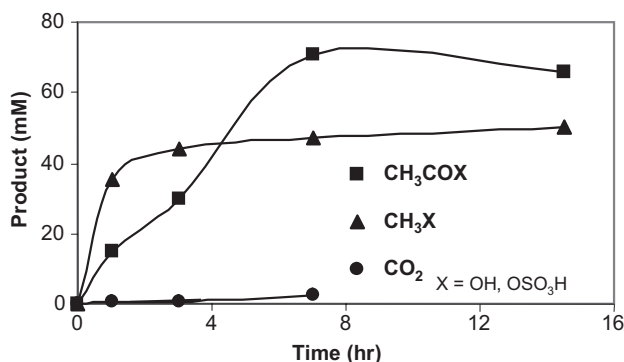


Figure 7. Time dependent product formation for Pd(II)-catalyzed oxidative condensation of methane directly to acetic acid.

This direct, oxidative condensation of methane to acetic acid in one-pot could be competitive with the current three-step, capital intensive process for the production of acetic acid based on methane reforming to CO, methanol synthesis from CO, and generation of acetic acid by carbonylation of methanol. Key improvements required with the $\text{PdSO}_4/\text{H}_2\text{SO}_4$ system, however, will be to develop more stable, faster, and more selective catalysts. Although it is possible sulfuric acid could be utilized industrially as a solvent and oxidant for this reaction, it would be desirable to replace sulfuric acid with a less corrosive material. This chemistry has recently been revisited, verified, and extended by Bell et al., who used $\text{Cu(II)}/\text{O}_2$ as the oxidizing system [22].

We are currently studying this reaction mechanism both experimentally and theoretically and believe the reaction proceeds via an ES C–H activation reaction to generate Pd-CH_3 intermediates, followed by oxidative carbonylation of Pd-CH_3 . We propose that this oxidative carbonylation occurs with either very low levels of free CO or coordinated CO, e.g. as Pd(CO)_x^{2+} species, that may be generated by slow over-oxidation of the methanol produced from the in-situ oxidation of methane. Some evidence for this is that added ^{13}CO and added $^{13}\text{CH}_3\text{OH}$ (in separate experiments) both react with $^{12}\text{CH}_4$ to generate, predominantly, $^{12}\text{CH}_3\text{ }^{13}\text{CO}_2\text{H}$. Addition of $^{12}\text{CH}_3\text{OH}$ to a $^{13}\text{CH}_4$ reaction mixture, moreover, generated primarily $^{13}\text{CH}_3\text{ }^{12}\text{CO}_2\text{H}$. Interestingly, although low levels of CO (added or produced by in-situ methanol oxidation) lead to the generation of acetic acid, addition of higher concentrations of CO essentially shuts down the reaction and only rapid formation of Pd black and CO_2 is observed.

These observations are all consistent with the proposed tandem-catalysis mechanism shown in Fig. 8. Central to this proposal is that the reaction proceeds via several parallel reaction steps as might be expected for formal eight-electron coupling of two methane molecules to acetic acid. The observation that the reaction is effectively stopped by high concentrations of added CO but proceeds at low levels of CO can be explained if the rate-limiting step is oxidation of Pd(0) by sulfuric acid. From independent experiments we have found that under high CO pressure

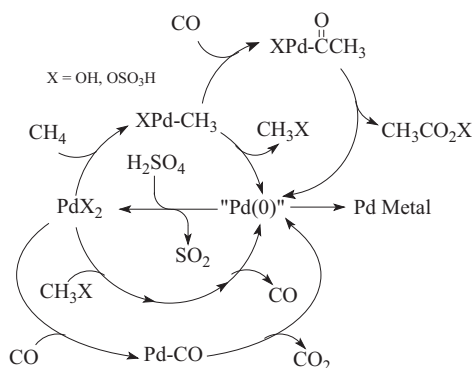


Figure 8. Proposed tandem-catalysis mechanism for oxidative condensation of methane directly to acetic acid.

conditions the rate of formation of Pd(0) is much higher than the oxidation of Pd(0) by sulfuric acid and the observed reaction inhibition under high pressures of CO is most probably because of loss of the active Pd(II) catalyst. Under low CO conditions, however, the rates of Pd(0) oxidation by sulfuric acid and Pd(II) reduction (from reactions with methane, methanol, and CO) are presumably balanced and the reaction can be maintained. These results are intriguing and suggest that CO insertion is particularly facile under these conditions of C–H activation. This could suggest that oxidative carbonylation of alkanes may be a particularly effective means of coupling C–H activation with a useful M–C functionalization reaction.

2.1.4.6 Summary

Significant progress has been made in incorporating the C–H activation reaction into a catalytic sequence to develop stable, active, selective systems for the direct, low temperature conversion of alkanes to functionalized molecules. Considering the state of knowledge today, while there is some understanding of how to incorporate the ES C–H activation reaction in poorly coordinating media, for example strong acid solvents, into catalytic cycles; less is known about facilitating the C–H activation reaction of alkanes in coordinating media such as water, and significantly less is understood of the other required catalytic steps that involve oxidative functionalization. This suggests that a greater level of fundamental understanding will be required to develop catalysts that:

- react with alkanes via the C–H activation reaction at useful rates in desirable solvents such as water;
- generate M–R intermediates that can be oxidatively functionalized at useful rates to generate a range of useful products;
- are more compatible with the C–H activation and the oxidative functionalization steps;
- are thermally stable under the reaction conditions required for generating useful products;
- are selective for generation of the desired products; and
- use practical oxidants that directly or indirectly use oxygen as the final oxidant.

Developing a basic understanding of these steps could lead to the development of the next generation of hydrocarbon conversion catalysts and new energy and petrochemical technologies.

Experimental Section

Oxidation of CH₄ to Methanol using Hg(II), Pt(II), and Au Cations

In a typical reaction, a 5 mL glass-lined, stirred, high-pressure reactor containing 20–50 mM of catalyst [HgSO₄, Pt(bpy)₂Cl₂ or 20-mesh Au powder] was added 3 mL 96 % H₂SO₄ with methane (pressure 300–800 psig). If Au was used H₂SeO₄

(3 M) was also added as an oxidant. The reaction mixture was vigorously stirred and maintained at 180 °C for 2 h. After cooling to room temperature, the reaction gas phase was analyzed by GC–MS and the liquid phase by ^1H and ^{13}C NMR spectroscopy and HPLC using internal standardization.

Pd(II) Catalyzed Oxidative Condensation of Methane to Acetic acid:

In a typical reaction, a 5-mL glass lined, stirred, high-pressure reactor is charged with 20 mM PdSO_4 , 2 mL 96 % H_2SO_4 , and 400 psig CH_4 . The reactor is heated to 180 °C for 2 h with stirring, cooled to room temperature, and analyzed as noted above.

2.2

Radical Halogenations of Alkanes

Peter R. Schreiner and Andrey A. Fokin

2.2.1

Introduction and Fundamental Examples

The light-induced radical chlorination of alkanes with elemental chlorine is one of the oldest organic reactions [1] and still is used industrially with methane [2]. This reaction is also important for atmospheric [3] and materials chemistry [4]. Free-radical chlorination is, however, impractical for higher alkanes because the discrimination between the primary (1°), secondary (2°), and tertiary (3°) C–H bonds is too low [5]. Chlorination in the condensed state is somewhat more selective, depending on the solvent used [6]. Direct fluorination of alkanes is difficult to control, because of high exothermicity and low energy barriers [7]. In contrast, the activation barriers are higher for brominations than chlorinations or fluorinations [8] resulting in appreciable bromination selectivity. Nevertheless, C–H bromination of strained hydrocarbons is often problematic because bromine radicals typically attack carbon atoms that lead to C–C bond-breaking and rearrangements [9]. Direct iodinations of unactivated C–H bonds of alkanes with I^\bullet are not possible, because of the overall endothermicity of this reaction, and all iodination methods are indirect (vide infra).

Substantial improvements of the selectivity of radical halogenations of alkanes may be achieved if free halogen radicals are *not* involved in the C–H activation step. Carbon-centered radicals are usually far more selective, because of polar and steric effects [10]. Even for the methyl radical the observed $3^\circ:2^\circ:1^\circ$ selectivity is 61:5:1 for small alkanes [11]. The involvement of the $^\bullet\text{CBrH}_2$ radical increases the selectivity further with or without metal catalyst (Table 1, entries 5 and 6). Simple trihalomethyl radicals are generated by photolytic [12], thermal [13], or heterogeneously catalyzed [14] decomposition of tetrahalomethanes. Although the alkane-activation step with $^\bullet\text{CHal}_3$ is more selective, selectivity is typically reduced because of the participation of halogen (Hal) radicals in the C–H abstraction, especially for Hal = Cl [15].

Table 1. Regioselectivity for functionalization of adamantane using halogen and carbon-centered radicals as the abstracting species.

Radical source/abstracting radical	Solvent, temperature	Initiation	Relative reactivity of 3°:2° C–H bonds
1 NBS/Br [•]	PhCl, 95 °C	(PhCO) ₂ O ₂	2.5 [16]
2 NBS + Br ₂ /Br [•]	CH ₂ Cl ₂ , 25 °C	<i>hν</i>	5.8 [17]
3 Br ₂ /Br [•]	H ₂ O/Cl(CH ₂) ₂ Cl, 100 °C	thermal	2.9 [17]
4 NCS/Cl [•]	C ₆ H ₆ , 80 °C	ABIN	2.5–3.7 [18]
5 CH ₂ Br ₂ /BrH ₂ C [•]	CH ₂ Br ₂ , 95 °C	(PhCO) ₂ O ₂	9.0 [16]
6 CH ₂ Br ₂ /BrH ₂ C [•] , [FeCl ₂ TPA] ^{b,2+}	CH ₃ CN, 25 °C	<i>t</i> -BuOOH	9.5 [19]
7 Cl ₂ /Cl [•]	CCl ₄ , 25 °C	<i>hν</i>	4.8 [20]
8 Br ₂ /Br [•]	CCl ₄ , 25 °C	<i>hν</i>	5.6 [18]
9 CCl ₄ /Cl ₃ C [•]	CCl ₄ , 95 °C	(PhCO) ₂ O ₂	24.3 [16]
10 CCl ₄ /Cl ₃ C [•]	CCl ₄	<i>t</i> -BuOOt-Bu	21.5 [18]
11 BrCCl ₃ /Cl ₃ C [•]	BrCCl ₃ , 95 °C	<i>t</i> -BuOOt-Bu	27 [16]
12 GIF + BrCCl ₃ /Cl ₃ C [•]	BrCCl ₃ /Py/AcOH 60 °C	<i>t</i> -BuOOH	8.2 [21]
13 BrCCl ₃ /Cl ₃ C [•] , H ₃ C [•]	Acetone	DMD ^a	18 [22]
14 <i>n</i> -C ₄ F ₉ I/ <i>n</i> -C ₄ F ₉ [•]	AcOH, 120 °C	<i>t</i> -BuOOH	16.6 [23]
15 CCl ₄ /Cl ₃ C [•]	CCl ₄ , 78 °C	PTC	28.5 [24]
16 CBr ₄ /Br ₃ C [•]	CH ₂ Cl ₂ , 25 °C	PTC	30.1 [24]
17 ClI ₄ /I ₃ C [•]	CH ₂ Cl ₂ , 25 °C	PTC	132.0 [24]

^a DMD = dimethyldioxirane

^b TPA = tris(2-pyridylmethyl)amine

For electrophilic and more bulky radicals, for example [•]C_nHal_{2n+1}, selectivity increases dramatically. Whereas the selectivity for the radical chlorination (Table 1, entry 7) and bromination (Table 1, entry 8) of adamantane with Hal₂ in CCl₄ is only approximately 5, for chlorinations with CCl₄ (Table 1, entries 9 and 10) and brominations with BrCCl₃ (Table 1, entry 11) the selectivity increases to 21.5–27. Halogenations under metal-catalyzed GIF conditions (Table 1, entry 12) or in the presence of dioxirane (Table 1, entry 13) are less selective, because of the participation of oxygen-centered (GIF) or methyl (DMD) radicals.

A new method for homolytic iodination of alkanes involves the homolysis of perfluoroalkyl iodides (for example *n*-C₄F₉I in the presence of catalytic amounts of

t-BuOOH) forming perfluoroalkyl radicals (e.g. $\cdot\text{C}_4\text{F}_9$) that are responsible for the C–H activation; the alkyl radicals abstract iodine atoms from perfluoroalkyl iodide in the propagation step [23, 25]. The 3°:2° selectivity of the iodination of adamantane with *n*-C₄F₉I/*t*-BuOOH is 17:1 [23], which is, however, slightly lower than for the BrCCl₃/*t*-BuOO*t*-Bu bromination (27:1) [16], in which Cl₃C \cdot is the abstracting radical. Other perfluoroalkyl radicals, generated from perfluoroalkyl iodides under mild conditions in the presence of radical starters (di-*tert*-butyl hyponitrite) [26], also give iodoalkanes. The branched radical *i*-C₃F₇ \cdot is substantially more reactive than linear *n*-C₄F₉ \cdot also indicating the importance of polar effects in the transition structures for hydrogen abstractions. The 2°:1° selectivity for *n*-heptane is higher than for the relatively selective *t*-BuO \cdot radical (vide supra) [26].

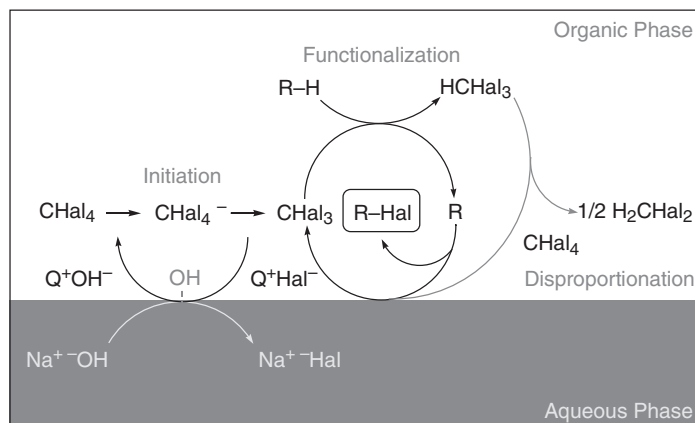
Our recently developed [24] phase-transfer catalytic (PTC) alkane halogenation procedure that is useful for chlorinations [27], brominations [28], and iodinations [29] of unactivated, aliphatic hydrocarbons provides an alternative and quite convenient way of generating the highly selective $\cdot\text{CHal}_3$ radicals. PTC-functionalization differ considerably from traditional free-radical alkane halogenations, because they do *not* involve highly reactive and therefore unselective halogen radicals. The C–H activation [30] selectivity for halogenations of adamantane is higher under PT conditions, because of the exclusive participation of $\cdot\text{CHal}_3$ radicals (Table 1, entries 15–17); the selectivity is the highest for any alkane radical halogenation reaction reported to date. Because this is currently one of the most practical alkane halogenation methods, in particular for iodinations (for example, the PTC procedure is currently used as an experiment in undergraduate organic chemistry laboratories) [31], this article focuses on this method.

2.2.2

Mechanisms

A typical PTC halogenation procedure involves a solution of the desired alkane in an inert organic solvent (dichloromethane, fluorobenzene, and others; liquid alkanes may also be used in excess without additional solvent) over a highly concentrated basic solution (for instance, 50 % NaOH) or solid inorganic base. A quaternary ammonium salt serves as the phase-transfer catalyst to transport the reagents among the phases. An arguably reasonable mechanistic proposal for these reactions involves the hydroxide ion as the initiator species, which may be extracted [32, 33] into the organic phase where it is highly activated, because of partial loss of its solvating water molecules. Hence, the hydroxide ion reduces the tetrahalomethane in a single-electron transfer step to the corresponding radical anion; such electron-transfer steps have been proposed for PTC-reactions involving CCl₄ [34]. The tetrahalomethane radical anion dissociates into halide and the respective trihalomethyl radical which abstracts hydrogen atoms from alkanes to produce alkyl radicals; these react with unused tetrahalomethane to produce the respective alkyl halide and a new chain-carrying $\cdot\text{CX}_3$ radical (Scheme 1). The haloform produced from the abstraction step also re-enters the cycle by base-initiated disproportionation [35, 36] into tetrahalomethane and dihalomethane. Hence,

the overall reaction produces the halogenated alkane and dihalomethane. The driving force is the formation of weaker C–Hal in place of stronger C–H bonds in the polyhalomethane reagent.

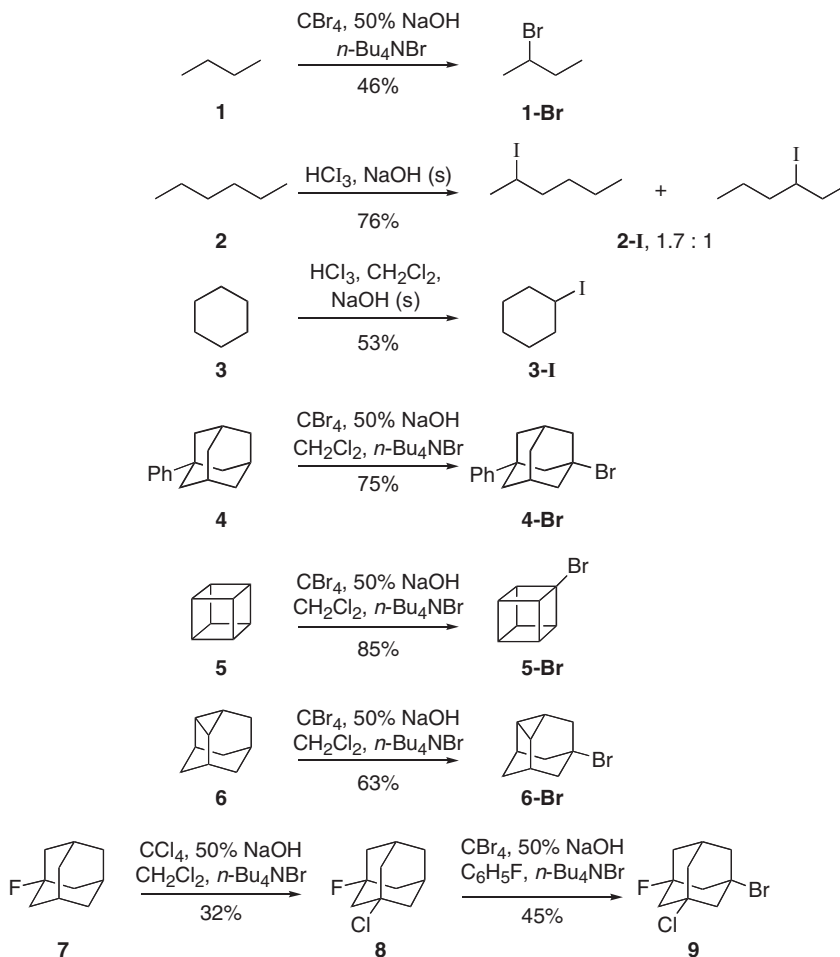


Scheme 1. Radical propagation cycle for single-electron transfer-initiated production of CX_3 radicals from CX_4 ($\text{X} = \text{Hal}$) and functionalization of an alkane (RH).

The kinetic deuterium/hydrogen isotope effects for cyclohexane and adamantane are approximately 5 [30] (in contrast with, for example, radical bromination of cyclohexane with Br^\bullet which gives a KIE value of approximately 2.4 [37] or 4 [38]) which shows that the transferred hydrogen atom lies about half-way between the carbon centers in the transition structure [30].

The PTC halogenations are favored in more polar media, probably because of the slightly increased solubility of polar components (catalyst, water) in the organic layer. Dichloromethane seems to play a special role, because the reactions with phase-transfer catalyst are only marginally faster than those without, and because this solvent actively participates in the mechanism, as is evident from the small amount of chloro products formed ($\leq 3\%$ at low CBr_4 concentrations). The effect of the catalyst is far more pronounced in all other solvents. The conversion rate of adamantane in the course of the PTC-bromination in fluorobenzene clearly depends on the NaOH concentration, with maximum rates at highest concentrations. These reactions can also be initiated by other bases (Li , K , Cs , Ba hydroxides), with a continuous increase in reactivity for the alkali metal hydroxides with increasing solubility in water, i.e., growing cation radius [39]. The catalyst plays a decisive role in PTC halogenations in fluorobenzene – because the initial rate of conversion is faster with increased alkyl chain lengths for the three tetraalkyl ammonium salts examined (tetraethyl, tetra-*n*-butyl, and tetra-*n*-octyl ammonium bromide), transfer of the reactants across the phase boundary must play an important role and hints at an extraction mechanism [33]. Although tetra-*n*-octyl ammonium bromide (TOctABr) has the highest initial rate, the activity of the catalyst is reduced in the course of the reaction, because of its degradation under the

strongly basic conditions. Hence, we found that tetra-*n*-butyl ammonium bromide (TBABr) is most suitable in these transformations.

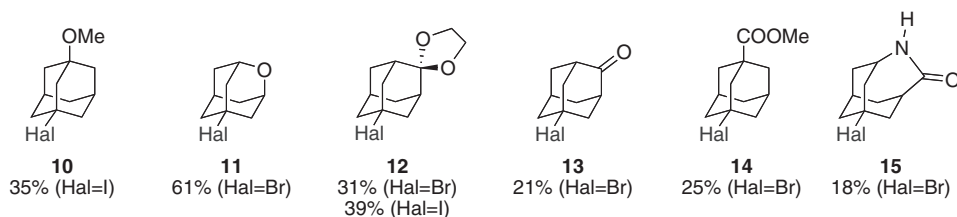


Scheme 2. A selection of PTC radical halogenations with linear, cyclic, and polycyclic alkanes.

2.2.3

Scope and Limitations

Non-activated methyl groups are never attacked in these reactions; toluene can be functionalized but isolation of the resulting benzyl halides from these PTC mixtures is difficult. Most remarkable is that strained hydrocarbons such as cubane (5) or 2,4-didehydroadamantane (6) can also be halogenated with conservation of the cage [27], in marked contrast with the halogenation reactions of these substrates with halogen radicals [40]. Dihalogenations with either the same or a differ-



Scheme 3. Range of halogenation reactions under phase-transfer catalytic conditions; halogenated products from the respective starting materials. The reaction conditions are similar to those presented above for

alkanes; absolute yields are given (not run to full conversion to avoid polyhalogenation, unreacted starting materials were recovered almost quantitatively).

ent halogen (7–9) are also possible showing that exchange (as often found for halogen radicals) [36] does not occur as readily in these reactions.

Although we initially focused on alkanes only, we have begun studying functional group tolerance in the functionalization of unactivated compounds using our PTC method. As adamantane derivatives were studied most extensively (but not exclusively) and are ideal model substrates for these types of study, we examined the reactions of the corresponding ethers (**10** and **11**), acetal **12**, and non-enolizable ketone **13**, methyl ester **14**, and amide **15** (Scheme 3) under conditions very similar to those described above. The halogenation of **12** is particularly encouraging because ketones can thus be protected and functionalized in positions more remote than C_{α} . The relatively long reaction times of our original procedure for the iodination of alkanes under PTC can be significantly shortened by ultrasonication [41].

There are several important preparative advantages [42] of our PT catalytic approach over other halogenation methods. First, a relatively inexpensive iodination reagent (HCl_3) can be used. Brominations with the brominating agent CBr_4 occur with high yields and several functional groups are tolerated. The C–H bonds of highly strained hydrocarbons are halogenated *without* concomitant rearrangements of the cages. Remarkably, otherwise impossible polyhalogenations without halogen exchange could be achieved [27, 42].

Experimental

Bromination of Cubane [27]

A mixture of 208 mg (2 mmol) cubane, 1.28 g (4 mmol) CBr_4 , 5 mL CH_2Cl_2 , 3 mL 50 % aqueous NaOH, and 25 mg tetrabutylammonium bromide was stirred at room temperature for 24 h then diluted with 10 mL of water and extracted with CH_2Cl_2 (3×5 mL). The extracts were washed with water and dried over Na_2SO_4 . Excess CH_2Cl_2 was removed at atmospheric pressure. Column chromatography (silica/pentane) gave 20 mg cubane and 274 mg (75 %) bromocubane identical, according to NMR [43] and MS [44] data, with material described previously.

Iodination of Cyclohexane

A 250-mL round-bottomed flask equipped with a magnetic stirring bar was charged with 150 mL cyclohexane, 65 g (0.62 mol) NaOH, and 9.0 g (0.023 mol) iodoform and closed with a polished cap. The mixture was stirred vigorously for 48 h at 25 °C. The mixture was then filtered and the precipitate was washed with pentane. The filtrate was evaporated under reduced pressure (300 mm) and 2.8 g crude product was obtained. Vacuum distillation (75–77 °C 17–19 mm Hg, Lit. 68–70 °C 10 mmHg) gives 2.5 g iodocyclohexane (0.012 mol, 53 % relative to iodoform).

Iodination of Adamantane

In a 25-mL screw-capped vial 1.36 g (0.01 mol) adamantane, 0.16 g tetrabutylammonium bromide (0.001 mol), and 3.94 g iodoform were dissolved in 15 mL CH₂Cl₂. Sodium hydroxide solution (aq., 50 %, 5 mL) was then added and the vial was equipped with a magnetic stirring bar. The mixture was heated with an oil bath at 40 °C with vigorous stirring for 72 h. The organic layer was separated and the aqueous solution extracted with pentane (5 × 25 mL). Removal of the solvents under reduced pressure and column chromatography of the residue (pentane, silica gel) gave 1.36 g (0.0052 mol) 1-iodoadamantane (52 %, TLC: R_F = 0.47) and 0.78 g (0.0020 mol) 1,3-diiodoadamantane (20 %, TLC: R_F = 0.25).

Acknowledgment

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2.3

Preparative SET C–H Transformations of Alkanes

Andrey A. Fokin and Peter R. Schreiner

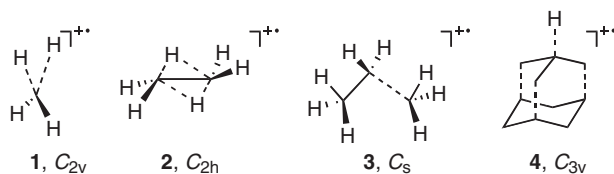
2.3.1

Introduction and Fundamental Examples

Owing to low-lying HOMOs the oxidation potentials of saturated hydrocarbons are quite high (usually >9 eV) and direct single-electron transfer (SET) oxidation requires the use of strong oxidants. When an electron is removed from a bonding σ -orbital, the ionized species are denoted σ -radical cations [1] which usually have a definite structure with one or several partially broken (elongated) σ -bonds [2, 3]. If the HOMO of the hydrocarbon is degenerate, the resulting radical cation distorts in accordance with the Jahn–Teller theorem. Detailed studies of these distortions requires both static and dynamic quantum-mechanical treatment, because of nonadiabaticity. Computations on the structures and transformations of hydrocarbon σ -radical cations are still formidable challenges [4]. Notwithstanding these complicating factors, analysis of the structures and transformations of fully relaxed σ -radical cations in their ground states

is quite instructive. The simplest alkane radical cation derived from T_d -methane distorts to lower symmetry, because of a triply degenerate HOMO. The substantial geometrical changes on relaxation increase the energy gap between the vertical (IP_v) and adiabatic (IP_a) ionization potentials of methane (13.6 compared with 12.6 eV). The C_{2v} -symmetry (Scheme 1) of $CH_4^{\bullet+}$ (**1**) with two elongated C–H bonds is supported both experimentally [5] and theoretically [6]. Ethane is also Jahn–Teller-active and distorts on ionization to a “diborane-like” C_{2h} -structure (**2**) [7]; the IP_v/IP_a gap is already much lower ($IP_v = 12.0$, $IP_a = 11.5$ eV) than that of methane. Both **1** and **2** are highly fluxional [8], because the barriers to topomerization are low.

Secondary distortions may also affect the structures of σ -radical cations. Although C_{2v} -propane does not have HOMO degeneracy its radical cation relaxes after ionization to a C_s -symmetrical structure; the C_{2v} form is not a minimum [9]. Higher alkanes can form a number of ionized forms with elongated C–C bonds, because of analogous second-order distortions. Usually, because of a limited number of σ -bonds that participate in the spin/charge delocalization, the experimental observation of the radical cations derived from linear alkanes is difficult [10]. The oxidation potentials of alkanes depend on their size; small cyclic alkanes usually have lower oxidation potentials (9.8–9.9 eV) than linear alkanes (10.2–10.5 eV) of comparable molecular weight. For higher cyclic and acyclic alkanes the IP are virtually identical (9.7–9.9 eV); branching usually reduces the IP only slightly. Strain energy affects the IP of hydrocarbons dramatically. Although, usually, strained hydrocarbons are more readily oxidized, there is no direct correlation between strain energies and IP. Ionization of strained hydrocarbons usually leads to substantial structural changes and the gaps between the IP_v and IP_a are quite high (up to 1 eV). The IP_a values correlate very well with the electrochemical half-wave oxidation potentials [11].



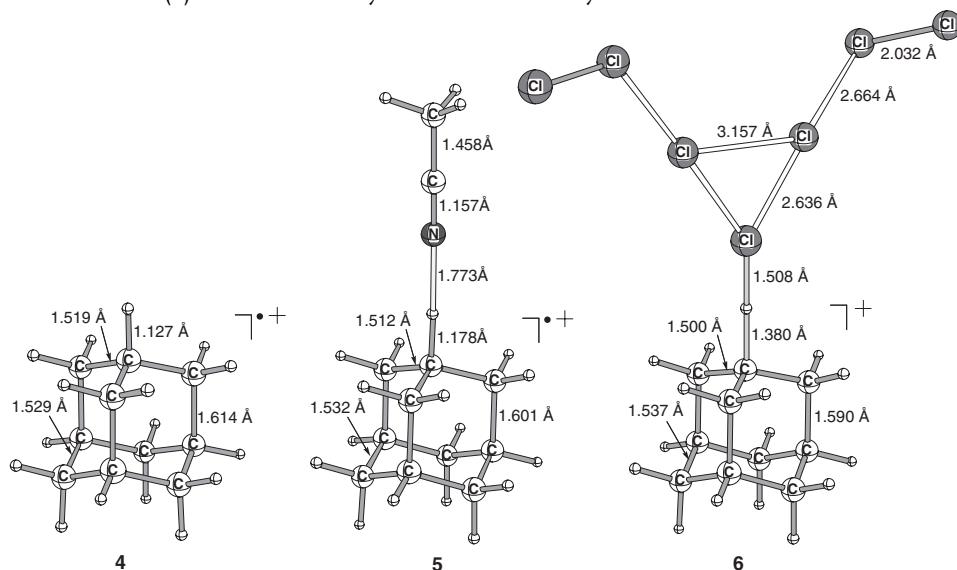
Scheme 1. The structures of representative alkane radical cations.

In contrast with small and, usually, strained alkanes, the HOMO of polycyclic relatively unstrained saturated hydrocarbons involve several C–C bonds. These hydrocarbons are usually quite reactive toward oxidants and have relatively low IP_v values (because of highly-lying HOMO) and IP_a (because of substantial delocalization in the radical cations). For example, adamantane elongates several bonds after ionization: the C_{3v} form of the adamantane radical cation (**4**) [12, 13] has *three* elongated C–C and one long tertiary C–H bond (Scheme 1).

Being high-energy species, σ -radical cations may undergo either bond breaking or H_2 loss (to alkene radical cations) or they rearrange [2]. Because of the high solvation energy of the proton, the most typical follow-up transformation of σ -radical cations in solution involves deprotonation forming alkyl *radicals* (Eq. 1). The Brønsted acidity of alkane radical cations approaches that of mineral acids [14, 15].



If the hydrocarbon radical cation has a definitive structure, proton loss occurs from one particular, well-defined position and these transformations are *more selective* than the alternative C–H abstractions from alkanes with radical reagents (Eq. 2). For example, C–H substitutions of the adamantane cage with radical reagents *always* give mixtures of 1 and 2-substituted adamantanes [2]. As the adamantane radical cation (**4**) has one single structure, proton transfer from the radical cation to the solvent occurs highly selectively. Scheme 2 shows the geometry of **4** and the structure of the complex of the adamantane radical cation with acetonitrile (**5**) where the tertiary C–H bond is already half-broken.



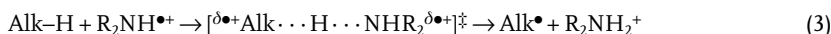
Scheme 2. The structure of the adamantane radical cation (**4**), its complex with CH₃CN (**5**), and the transition structure for H-coupled electron transfer from adamantane to model electrophile Cl₂⁺ (**6**) at B3LYP/6–31G*.

2.3.2

Mechanisms

The generation of σ -radical cations from saturated hydrocarbons requires very strong SET oxidizers. The oxidation reactions can be accomplished by chemical electron transfer (CET), photochemical electron transfer (PET), and anodic oxidation. The oxidation potentials of stable, organic CET oxidants, e.g., commercially available tris(4-bromophenyl)amminium hexachloroantimonate (TBA⁺SbCl₆[−]) or tris(2,4-dibromophenyl)amminium hexachloroantimonate (TDA⁺SbCl₆[−]), are too low (1.06 and 1.50 V

relative to SCE, respectively) to oxidize unstrained alkanes. Only very strained hydrocarbons, for example bicyclo[3.1.0]pentane[16] or quadricyclane[17], undergo CET with these oxidants. The aminium radical cations $\text{Alk}_2\text{NH}^{\bullet+}$, generated in situ from Alk_2NCl and H_2SO_4 , are slightly more powerful SET acceptors (computed oxidation potentials are ca 8.5 eV) than $\text{Ar}_3\text{N}^{\bullet+}$. However, $\text{Alk}_2\text{NH}^{\bullet+}$ oxidants react with alkanes as hydrogen abstractors rather than SET oxidizers [18, 19]. Polar contributions to the mechanism are substantial, because the hydrogen abstraction is believed to occur via radical–cationic transition structures (Eq. (3); $\text{R} = \text{Me}$, 2-Pr) and where the selectivity is determined by the geometry of the alkane radical cation. For linear alkanes, which form a number of isomeric radical cations, mixtures of substituted positional isomers form [20]. For adamantane, which forms a single radical cation structure (4) with an elongated tertiary C–H bond (see above), the functionalization at the bridgehead position with $\text{Alk}_2\text{NH}^{\bullet+}$ is highly selective [18] because this mode of attack agrees with concomitant polarization of the adamantane cage.

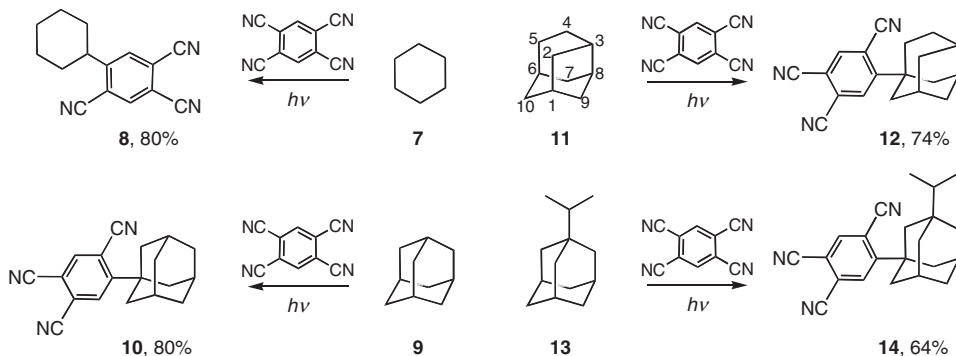


A similar mechanism (Eq. 4) is operative in reactions of saturated hydrocarbons with closed-shell oxidizing electrophiles ($\text{E} = \text{Hal}_n^+$, NO_2^+ , etc.) where the H-transfer from a C–H bond is accompanied by an ET through the linearly H-coupled fragment (H-coupled electron transfer) [13]. The hydrocarbon part of the transition structures resembles the respective radical cation (that for the reaction of adamantane with Cl_7^+ is shown (6) in Scheme 2) [13].

For non-electrophilic strong oxidants, the reaction with an alkane typically follows an outer-sphere ET mechanism. Photoexcited aromatic compounds are among the most powerful outer-sphere oxidants (e.g., the oxidation potential of the excited singlet state of 1,2,4,5-tetracyanobenzene (TCB) is 3.44 V relative to the SCE) [14, 15]. Photoexcited TCB (TCB^*) can generate radical cations even from straight-chain alkanes through an SET oxidation. The reaction involves formation of ion–radical pairs between the alkane radical cation and the reduced oxidant (Eq. 5). Proton loss from the radical cation to the solvent (Eq. 6) is followed by aromatic substitution (Eq. 7) to form alkylaromatic compounds.



The photoinduced oxidation with TCB is among the most selective C–H substitutions of aliphatic compounds. For example, oxidation of cyclohexane (7) with TCB in acetonitrile gave 8 as the sole product [14]. Many saturated acyclic hydrocarbons have been oxidized with moderate to good selectivity [14]. Oxidation of adaman-



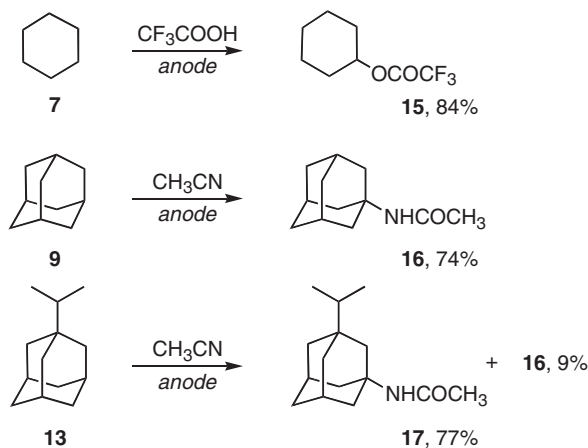
Scheme 3. C–H bond substitutions of saturated hydrocarbons with photoexcited TCB.

Anodic oxidation of alkanes is a viable alternative means of generating σ -radical cations from alkanes [23]. In contrast with oxidations with short-lived photoexcited species, electrooxidation of the substrate absorbed on the anode involves two consecutive ET steps – oxidation of the alkane then deprotonation to an alkyl radical (Eq. 8) and further oxidation of the alkyl radical to a carbocation (Eq. 9).



Alkyl cations thus formed may recombine with the nucleophile (Eq. 10) giving trifluoroacetates or acetamides under anodic oxidation conditions in CF_3COOH or CH_3CN , respectively. For example, electrooxidation of cyclohexane (**7**) in $\text{CH}_2\text{Cl}_2/\text{CF}_3\text{COOH}$ yielded 84 % cyclohexyl trifluoroacetate (**15**) [23]; oxidation of adamantane (**9**) gave acetamide (**16**) cleanly (Scheme 4) [24].

In general, electrooxidations in which intermediate alkyl cations may undergo rearrangements and/or fragmentations are *less* selective than photoinduced SET oxidations. For example, the photoinduced oxidation of protoadamantane with TCB gave a single product (**12**, Scheme 3) whereas a mixture of isomeric acetamides is formed in the electrooxidation in CH₃CN [25]. Although the TCB oxidation of alkyladamantane **13** (Scheme 3) selectively yielded **14**, partial fragmentation of hydrocarbon **13** occurs under anodic oxidation conditions (Scheme 4).



Scheme 4. Anodic oxidation of saturated hydrocarbons.

2.3.3

Scope and Limitations

C–H transformation of alkanes by SET is still a developing area of preparative organic chemistry. Generation of σ -radical cations from alkanes in solution requires strong oxidants, and is achieved by photochemical and electrochemical oxidation. Under these conditions even unstrained strained alkanes may be functionalized readily. The C–H substitution is selective if the hydrocarbon forms a radical cation with a definite structure and/or deprotonation from a certain C–H position of the radical cation dominates. Overoxidations are the most typical side reactions that lead to disubstituted alkanes. This can usually be avoided by running the reactions at low alkane conversions.

Experimental

Photooxidation of Cyclohexane (7) [14]

A solution of TCB (71 mg, 0.4 mmol) and cyclohexane (336 mg, 4 mmol) in 40 mL acetonitrile was irradiated for 4 h, under argon, with a multilamp reactor fitted with six 15-W phosphor-coated lamps (maximum emission at 320 nm). The reaction mixture was concentrated in vacuo. Chromatographic separation on silica gel (*c*-C₆H₁₂/EtOAc, 8:2) gave TCB (20 mg, 0.32 mmol), and 57 mg (0.24 mmol, 80 %) 5-cyclohexyl-1,2,4-tricyanobenzene (8), as colorless crystals (m.p. 125–126 °C, EtOH). ¹H NMR (CDCl₃, 400 MHz): δ 1.2–1.6 (m, 5H), 1.8–2.0 (m, 5H), 3.08 (tt, *J* = 12 and 3.5 Hz, 1H), 7.85 (s, 1H), 8.05 (s, 1H) ppm. ¹³C NMR (CDCl₃, 400 MHz): δ 25.3, 26.0, 33.0, 43.1, 113.6, 114.0, 114.2, 114.5, 117.1, 119.4, 132.1, 137.0, 157.2 ppm. C₁₅H₁₃N₃; calcd. C 76.57; H 5.57; N 17.86.; found C 76.3, H 5.8; N 17.5.

Photooxidation of Protoadamantane (11) [21]

A solution of **11** (400 mg, 2.94 mmol) and TCB (315 mg, 1.76 mmol) in acetonitrile (400 mL) was irradiated for 3 h, under argon, at 20 °C with a 450-W mercury lamp (maximum emission at 350 nm). The reaction mixture was diluted with water (40 mL) and the solvents (with unreacted protoadamantane **11**) were removed under vacuum. Chromatographic separation on silica gel (*c*-C₆H₁₂/EtOAc, 7:3) gave TCB (160 mg, 0.89 mmol), and 183 mg (0.64 mmol, 74 %) 5-(6-protoadamantyl)-1,2,4-tricyanobenzene (**12**, *R*_F = 0.55) as colorless crystals (m.p. 232–234 °C, acetonitrile). ¹H NMR (CDCl₃, 400 MHz): δ 1.42 (m, 1 H), 1.72 (m, 7 H), 1.86 (m, 1 H), 2.12 (m, 1 H), 2.34 (s, 1 H), 2.47 (m, 3 H), 2.70 (m, 1 H), 7.80 (s, 1 H), 8.05 (s, 1 H) ppm. ¹³C NMR (CDCl₃, 400 MHz): δ 24.2, 32.7, 34.4, 35.6, 35.9, 36.0, 39.9, 40.9, 43.2, 113.5, 113.7, 114.5, 115.7, 117.0, 119.2, 131.0, 139.5, 162.0 ppm. IR (CHCl₃): ν 2850–2290 (C–H), 2230 (C–N), 1590–1650 (C–C) cm^{−1}. C₁₉H₁₇N₃: calcd. C 79.41; H 5.96; N 14.62.; found C 79.25, H 6.16; N 14.43.

Acknowledgment

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2.4**Photochemical Processes****2.4.1****The Mercat Process**

Robert H. Crabtree

2.4.1.1 Introduction and Fundamental Examples

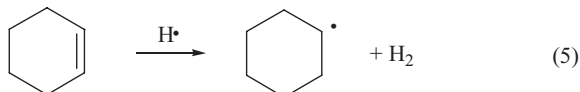
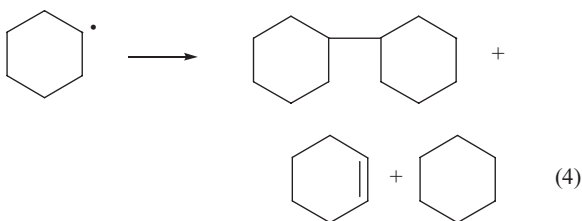
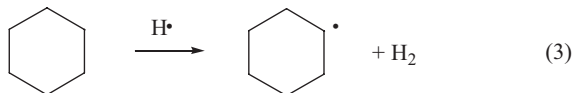
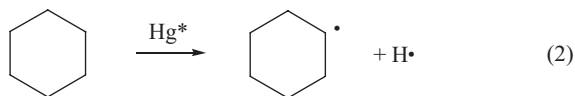
The term “Mercat reaction” refers to the use of mercury photosensitization to perform reactions on a preparatively useful, multigram scale. Typically these reactions involve CH activation, for example the conversion of methanol to ethylene glycol or indeed almost any organic compound to its dehydro dimer.



These reactions require stoichiometric input of photons and most of the conversions achieved are endothermic. Fortunately the quantum yields are very high (0.2–0.8).

The general principles of Hg photosensitization are fully discussed in Calvert and Pitts text[1], and the early history of the subject is covered in a 1963 article by Gunning and Strauss[2]. Briefly, a low-pressure mercury-vapor lamp produces 254 nm radiation that is absorbed by trace mercury in the vapor phase of a quartz photoreactor. A drop of mercury can be added to the reactor to ensure enough Hg vapor is present. The mercury atom in the reactor is excited to the relatively long-lived (ca 10^{−7} s) ³P₁ state, denoted Hg*; this is the reactive species that attacks the organic substrate.

The critical property of the Mercat process [3–8] that gives it its selectivity is that only Hg atoms in the vapor phase undergo reaction, because their absorption line is narrow and matched with the sharp emission line of the lamp. Mercury dissolved in the liquid phase has a broadened and shifted absorption band and Hg* in solution has a short excited-state lifetime, so the liquid phase undergoes no significant reaction. In the vapor, Eqs. (2)–(5) produce the dehydro dimer, which condenses.



Because the vapor alone is reactive, only volatile monomers, for example MeOH, react and involatile dehydro dimers, for example (CH₂OH)₂ remain in the liquid phase and are thus protected from further reaction. The substrate in the reaction is normally heated under reflux to maximize the rate of reaction; once again essentially only the monomer is volatile, even under reflux.

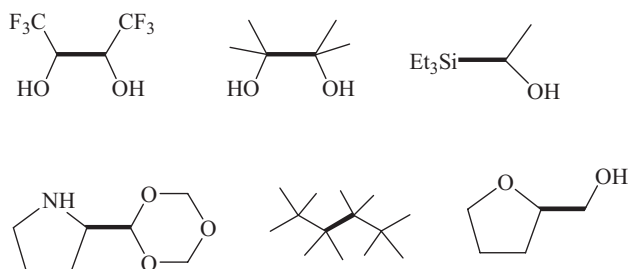
Intense activity in the field during the period 1945–1973 had an almost exclusively physicochemical focus, so the preparative advantages of the method were not recognized. The low pressures used in this work meant that vapor pressure selectivity effects of the sort discussed above were not apparent. In addition, the substrates chosen did not include a wide range of functional groups. A few applications [9, 10] to both organic and inorganic synthesis were reported in this period, however.

In looking at some control reactions for transition-metal catalyzed alkane photodehydrogenation, we came across mercury-photosensitized dehydrodimerization of alkanes. The very high efficiency of the procedure, when performed under reflux conditions at ambient temperature and pressure was immediately obvious.

Under our standard conditions [5], with reflux under N₂ (Hg* conditions), Hg* is the reactive species which attacks the substrate. C–H bond scission produces C-centered radicals and H atoms. The H atoms do not recombine but tend to

abstract H from the substrate, fortunately with a selectivity ($3^\circ > 2^\circ > 1^\circ$) very similar to that of Hg^* itself, to give further C-centered radicals. These recombine and disproportionate. The dehydro dimer condenses and is protected from further reaction but the alkene product of disproportionation, which is normally a major byproduct in conventional radical reactions, remains in the vapor and is rapidly converted back into C-centered radicals by attack of H atoms. Any alkene formed is therefore rapidly recycled into the radical pool. These reactions are shown for cyclohexane in Eqs. (2)–(5). Even relatively involatile substrates react, for example, we successfully dimerized $n\text{-C}_{18}\text{H}_{38}$ at 200°C in vacuo or with steam distillation at 100°C .

Alcohols, ethers and certain amines also react and a broad series of compounds can be conveniently synthesized by the dimerization procedure. Typical examples are shown in Scheme 1, in which the new bond formed is marked in bold. For alcohols, ethers, and amines, highly selective attack at a C–H bond α to a heteroatom is observed. In cases where two different substances react, the two homo dimers and the hetero dimer are all formed. This can still be synthetically useful because the three compounds are often sufficiently different, either in polarity or volatility, to be readily separable by chromatography or fractional distillation.



Scheme 1. Some products formed under Hg^* conditions. The newly formed bond is shown in bold.

Trioxan gives a protected aldehyde as product. For example, the cross-dimer from trioxan and cyclohexane gives $\text{C}_6\text{H}_{11}\text{CHO}$ on hydrolysis. The overall process is equivalent to an alkane carbonylation. Likewise, a protected form of proline is formed from trioxan and pyrrolidine.

Study of the mixed substrate systems shows that the reactivity of a given bond depends on its bond strength and on the volatility of the substrate in question. If the bond strengths are known, we can estimate the product ratio to be expected. Otherwise, we can estimate them using an equation that originally appeared in patents by Cier [11]. In instances, for example n -octane, in which a large number of C–H bonds of similar strength are present, attack is observed at all the 2° C–H bonds, and statistical recombination of the radicals occurs. The resulting materials have a very low freezing point for their molecular weight, a feature that could lead to practical applications.

Alkane-derived radicals can also be trapped by neutral molecules, for example CO, SO_2 , or O_2 . From CO, we find that R_2CO is the major product formed. From

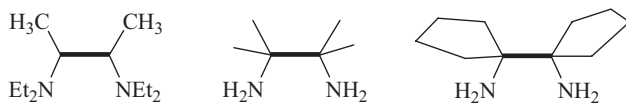
SO₂, a mixture of species is obtained, but oxidation produces the sulfonic acid, RSO₃H, in good yield [8a]. Molecular oxygen gives the hydroperoxide, ROOH [8b].

The standard Hg* conditions fail with substrates in which the Hg* attacks a functional group, rather than a C–H bond. Hg* has a stronger affinity for lone pairs and π -bonds than for σ -bonds, as suggested by the studies of Duval et al. [12]. With its s^1p^1 electronic configuration, Hg* can bind to a lone pair donor such as NH₃ via a 3e bond, nominally of half-order. The known Hg*–NH₃ binding energy of 17 kcal mol^{–1} is consistent with this idea. The proposed origin of X–H bond cleavage can best be illustrated by the example of H₂. In this case, transfer of one electron from H₂(σ) to the Hg p orbital, combined with one-electron transfer from the Hg p orbital to H₂(σ^*) could lead to a reduction of H–H bond order to zero [13].

Ketones, esters, carboxylic acids and most amines behave poorly under Hg* conditions. Arenes are interesting in that cleavage of the weak benzylic C–C bond is a significant pathway under these conditions (Eq. 6). The Hg* may bind to the arene ring in a π -fashion as an exciplex and transfer its energy to the molecule as a whole [14].

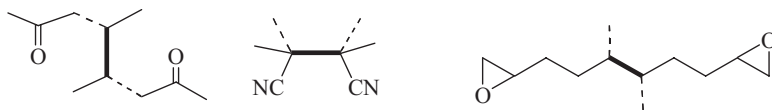


To deal with instances in which the standard Hg* conditions fail, we turned to the addition of a reactive gas, typically H₂ [6], to intercept the Hg* before it has time to “misbehave”. Under optimum conditions, when $p(\text{H}_2)$ is approximately 660 mmHg and $p(\text{substrate})$ is approximately 100 mmHg, H₂ is far more reactive than the substrate. H atoms now take over from Hg* as the active abstractor; these have little or no tendency to attack functional groups. Instead they either abstract the desired H atom from the weakest C–H bond or they add to the C=C bond of an alkene to give the same types of C-centered radicals formed in Eq. (5). The presence of lone pairs or π -bonds in the substrate apparently does not interfere significantly and a much wider range of substrates can now be dehydrodimerized. NEt₃ fails to react under Hg* conditions, presumably because Hg* attacks the N lone pair and energy transfer leads to thermal excitation of the substrate but not to productive chemistry. Under Hg*/H₂ conditions, the weak C–H bonds α to nitrogen are now abstracted and the dehydro dimer is formed, again with vapor-pressure selectivity. Scheme 2 shows some of the compounds that can be formed in this way. Quantum yields of 0.04–0.8 are usual and for most substrates values are in the range 0.2–0.6. Chemical yields are good to excellent (40 % to 98 %). Arenes still behave poorly, however, probably because H atom addition leads to undesired and unselective partial saturation of the aromatic ring.



Scheme 2. Some products formed under Hg*/H₂ conditions. The newly formed bond is shown in bold.

H atoms attack alkene C=C bonds (Eq. 5), because Hg/H_2 conditions also convert alkenes. Scheme 3 shows examples in which the dotted bond shows the site of the original C=C bond and the bold line represents the new C–C bond. Proper choice of the position of the double bond in the substrate enables formation of a radical center at a defined location along a chain, resulting in the formation of a defined compound rather than a mixture.

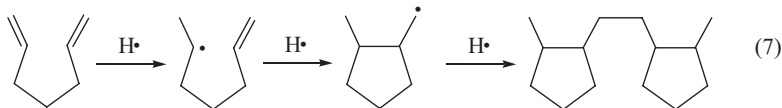


Scheme 3. Hydrodimerization products formed under Hg^*/H_2 conditions. The newly formed bond is shown in bold; the C=C bond position is dotted.

With the Hg^*/H_2 /alkene method we could prepare specific dimers and so identify them in the mixture of products formed from saturated analogs. Under Hg^* conditions, *n*-butanol forms the α,α , α,β , and α,γ -dimers, but authentic samples were not available for comparison. Authentic samples were obtained in a series of Hg^*/H_2 reactions; $\text{CH}_2=\text{CHCH}_2\text{CH}_2\text{OH}$ alone gave the γ,γ -dimer, $\text{CH}_3\text{CH}=\text{CHCH}_2\text{OH}$ gave the β,β -, β,γ -, and γ,γ -dimers, and $\text{CH}_3\text{CH}_2\text{CH}=\text{CHOMe}$ gave the α,α -, α,β -, and β,β -dimers. Comparisons of the products formed in this and related experiments enabled identification of all the dimers [13].

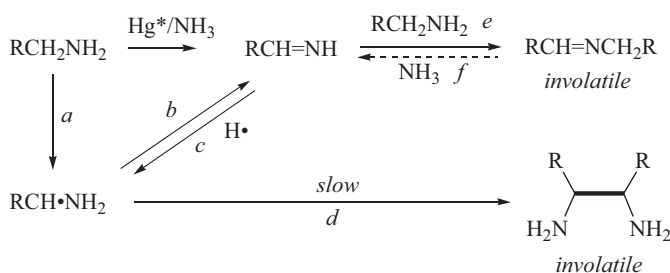
Fluoroalkenes, $\text{RCF}=\text{CF}_2$ add H at the terminal position and the resulting dimer is the 2,2' isomer. The terminal H substituents are clearly identifiable in the ^1H NMR spectrum of the product, confirming the mechanistic pathway.

$t\text{-BuCH}=\text{CH}_2$ also gave a small amount of material derived from 1,2-methyl migration in the intermediate radical, in addition to the expected hydro dimer. Such radical rearrangements do not usually take place, but here we have a large amount (ca. 40 kcal mol^{-1}) of excess thermal energy that is hard to dissipate in the vapor. As expected from this, addition of a powerful quencher of vibrational energy, for example CO_2 , results in significant quenching of the rearrangement. Radicals normally add to C=C double bonds, but this is not very efficient in the intermolecular reaction, because we do not see the expected products from this pathway under Hg^* conditions or we would see a more unsymmetrical dimer, for example $\text{RCH}_2\text{CH}_2\text{CH}(\text{Me})\text{R}$ from $\text{R}^\bullet\text{CH}-\text{CH}_2$. This can be a major pathway in intramolecular reactions, for example that of the diene shown below. H atoms and the resulting C-radical are now set up to cyclize; indeed, the resulting cyclic dimer is now the major species (Eq. 7).



Not all substrates reacted cleanly under Hg^*/H_2 conditions. Many amines fell into this class. Substrates with strong ($>98\text{ kcal mol}^{-1}$) C–H bonds, for example

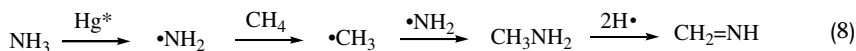
methane, ethane and di-*t*-butyl, also failed to react. Paul Krajnik, a postdoctoral associate in this group, suggested ammonia might be a useful reactive gas in such circumstances. He first tried it for primary amines; for these the major product under Hg^*/NH_3 conditions was the C-substituted imine. This suggests that the intermediate radicals are more likely to disproportionate (step b) than to dimerize (step d). The resulting unsubstituted imine is still volatile and so would be recycled by H-atom attack just as for alkane conversion, except that thermal condensation with the starting amine to give the C-substituted imine (step e) is rapid. The C-substituted imine, being involatile, is protected from H atom attack and survives to become the major product. N-centered radicals are also formed in the system but, for clarity, pathways involving this species have been omitted from Scheme 4.



Scheme 4. Some pathways under Hg^*/NH_3 conditions.

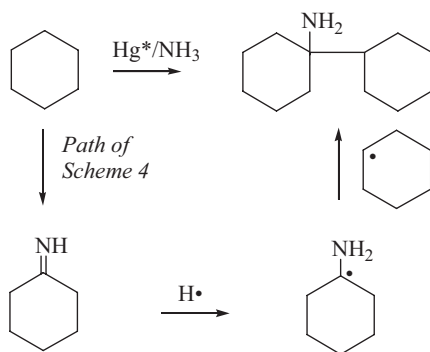
The presence of NH_3 enables step f and, by reversing step e, prevents the accumulation of the undesired C-substituted imine, so the dehydro dimer is obtained in good yield. The dimerization of *i*-Pr NH_2 gives the useful diamine $\text{H}_2\text{NCMe}_2\text{NH}_2$, previously only available in quantity by a tedious multistep route.

Methane (C–H bond strength $105 \text{ kcal mol}^{-1}$) reacts under Hg^*/NH_3 conditions, but only to give an involatile oil containing C, H, and N. This results from thermal oligomerization of an intermediate imine such as $\text{CH}_2=\text{NH}$. To avoid the problem we built a reactor to trap the initial products [7a]. The gases were rapidly recycled by means of a peristaltic pump through a cold trap at -20°C . This enabled trapping of the intermediate, $\text{CH}_2=\text{NH}$, probably formed by the following route (Eq. 8).



At slower gas recycle rates subsequent reactions of $\text{CH}_2=\text{NH}$ occur to give C_2 and C_3 imines. Initial formation of CH_2NH_2 by hydrogen atom attack on $\text{CH}_2=\text{NH}$, followed by recombination with CH_3 from methane, gives EtNH_2 . This is known to be converted into $\text{MeCH}=\text{NH}$ under Hg^* conditions, accounting for the C_2 imines. Repetition of these steps would give higher imines, with the final result being oligomerization and functionalization of methane. Few reactive gases can do this. They must bind well to Hg^* and have a bond energy of less than

112 kcal mol⁻¹ (the energy of Hg*) to be subject to bond scission. NH₃ has a bond energy of 107 kcal mol⁻¹ and is known to bind strongly to Hg* [12]. The mediator must have a bond strength greater than that of the substrate otherwise the fragments produced will not have the driving force necessary to abstract H from methane; again NH₃ meets this criterion.



Scheme 5. Cyclohexane amination under Hg^*/NH_3 conditions.

The proposed pathway is supported by the results obtained from Hg^*/NH_3 and cyclohexane. The major amine product is the interesting tertiary amine shown. This probably results from recombination of cyclohexyl with the radical derived from hydrogen atom addition to the imine (Scheme 5).

2.4.1.2 Industrial Applications

Mercury-photosensitized chemical reaction in the presence of aqueous ammonia (NH_4OH) has been found to be a simple and versatile method of introducing polar surface functionality comprising nitrogen and oxygen to polyolefins such as low-density polyethylene (LLDPE) and polypropylene (PP). Thus, nitrogen and oxygen surface functionality are introduced surface-selectively on LLDPE and PP to give a relatively hydrophilic surface, as revealed by XPS, ATR-IR, and water contact angle analyses [15]. Some other applications come from monomer synthesis in polymer chemistry [16].

2.4.1.3 Conclusion

Vapor pressure selectivity and other phase-specific reactions might be useful for achieving selectivity not possible by conventional means. The method makes reactive radicals such as H atoms available in preparatively useful amounts using only inexpensive apparatus. Alkanes can be functionalized in a variety of ways. Several unusual compounds are also available in this way from a variety of alcohols, alkenes, amines, carboxylic acids, ethers, and fluorocarbons.

Experimental

The substrate is heated under reflux with a drop of Hg in a quartz vessel illuminated with 254-nm light from a low-pressure Hg lamp until the desired degree of conversion has been achieved. The liquid product is poured from the mercury (dissolved Hg can be removed with Zn dust (excess, 1 h)) and the product is isolated by conventional distillation, chromatography, or crystallization, depending on the exact properties of the target compound. Yields from 85–95 % are typical. Details are given elsewhere [3–8].

Acknowledgment

I would like to thank the many coworkers who have contributed so importantly to the progress of this project, especially Mark Burk, Steve Brown, Cesar Muedas, Rich Ferguson, Paul Krajnik, and Demetrius Michos. We also thank the DOE for support.

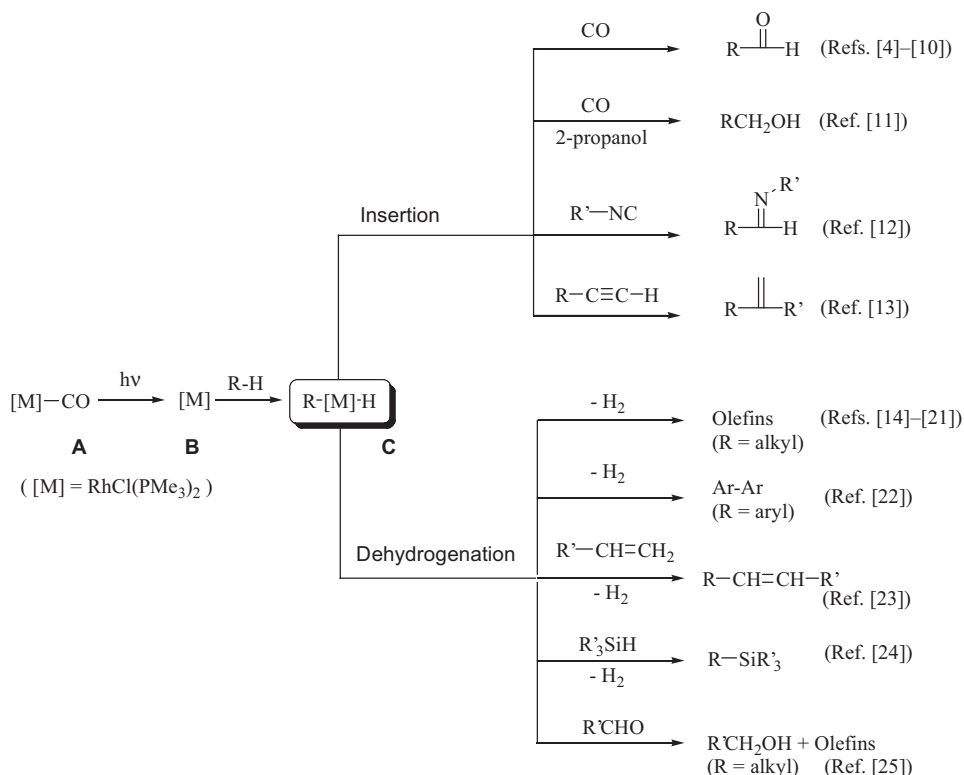
2.4.2

Rhodium-catalyzed C–H Bond Transformation Under Irradiation

Toshiyasu Sakakura

2.4.2.1 Introduction and Fundamental Examples

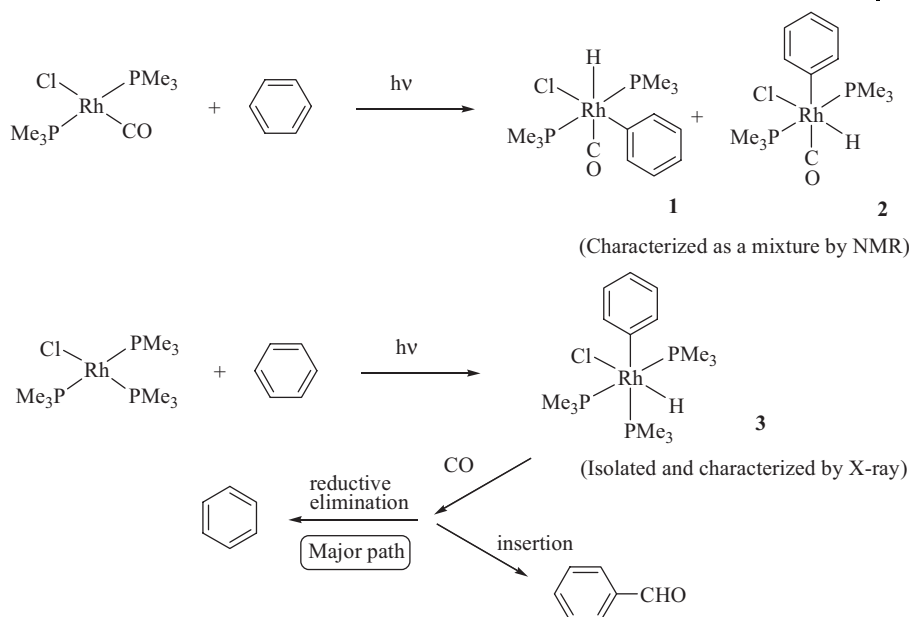
Organic synthesis is currently the science of the transformation of functional groups. Hydrocarbons without functional groups are difficult to convert under mild conditions. Moreover, reactions at high temperatures or under radical conditions produce complex mixtures. Hence, a dream of synthetic organic chemists is selective organic synthesis starting from unreactive hydrocarbons using highly sophisticated catalysts. In 1982, Bergman, Graham, and Jones and coworkers [1–3] first reported the oxidative addition of unreactive C–H bonds to low-valent transition metals. Although this methodology has received much attention for selective activation of hydrocarbons under mild conditions by a non-radical pathway, straightforward application of the resulting alkyl- or aryl(hydrido) complexes to “productive” catalytic reactions were unsuccessful, because the complexes were electronically and coordinatively saturated (18-electron and 6-coordinate). We have successfully developed “productive” C–H bond activation reactions based on a photo-assisted rhodium catalyst system using $\text{RhCl}(\text{CO})(\text{PMe}_3)_2$ as the catalyst precursor. The $\text{RhCl}(\text{CO})(\text{PMe}_3)_2$ system is highly catalytic (greater than a few thousand turnovers for dehydrogenation) and is applicable to a variety of reactions as summarized in Scheme 1 [4–25]. The initial idea of using a Vaska-type sixteen-electron, four-coordinate complex (**A**) as the catalyst precursor came from the desire to form coordinatively unsaturated hydridoalkyl complexes (**C**) by oxidative addition of a C–H bond so that (**C**) could react further. Hence, the preferred active species (**B**) before C–H oxidative addition is a fourteen-electron complex (Scheme 1). A similar idea was discussed by Felkin, Crabtree, and co-workers in their dehydrogenation studies of alkanes [26, 27]. The actual mechanism is discussed in the next section.



Scheme 1. Various transformations of hydrocarbons catalyzed by the $RhCl(CO)(PMe_3)_2$ system.

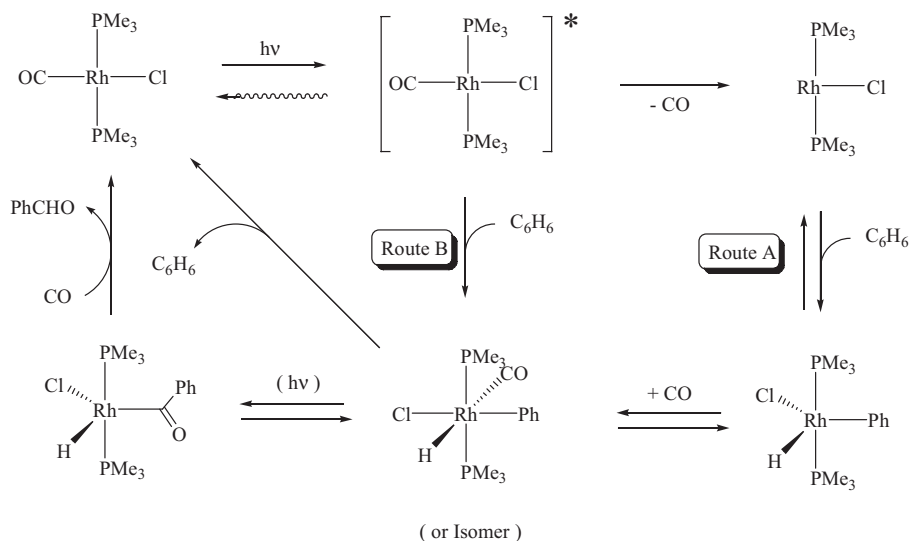
2.4.2.2 Mechanism

When photoirradiated the $RhCl(CO)(PMe_3)_2$ system drives C–H bond activation. The mechanism is, however, different from classic photo-driven C–H bond activations, for example the mercury-photon system, which includes a radical species as the key intermediate [28]. The very high primary C–H selectivity of the $RhCl(CO)(PMe_3)_2$ system as shown in the next section clearly reflects the non-radical mechanism. A possible common intermediate involved in Scheme 1 is an alkyl- or aryl(hydrido) complex formed by oxidative addition of hydrocarbons to $RhCl(PMe_3)_2$ or photo-excited $RhCl(CO)(PMe_3)_2$. In 1994, Field and Goldman independently investigated the reaction of $RhCl(CO)(PMe_3)_2$ with benzene when irradiating. The reaction gave a complex mixture that contained several new species, as indicated by NMR. Although the resulting hydrido species were too unstable to isolate, results from low-temperature NMR suggested the structures of the phenyl(hydrido) complexes **1** and **2** (Scheme 2) [29, 30]. Choi and Sakakura recently successfully isolated and unambiguously determined the structure of the phenyl(hydrido) complex **3**, obtained by reaction of Wilkinson-type complex, $RhCl(PMe_3)_3$ with benzene under irradiation [31]. Treating complex **3** with CO yielded benzene and benzaldehyde.



Scheme 2. Oxidative addition of C-H bonds to $\text{RhCl(CO)(PMe}_3)_2$ and $\text{RhCl(PMe}_3)_3$ under irradiation.

Dissociation of the carbonyl ligand was initially postulated as the role of the photon (Route A, Scheme 3) [4]. Mechanistic investigations by Goldman et al. indicated, however, that C-H bond oxidative addition to the photo-excited sixteen-electron



Scheme 3. Possible mechanism for benzene carbonylation by the $\text{RhCl(CO)(PMe}_3)_2$ system.

tron species seems reasonable at least for carbonylation (Route B) [30]. Ford reported that both the dissociative (Route A) and associative (Route B) mechanisms are operative for the carbonyl ligand, as judged by time-resolved flash photolysis [32]. The effects of the wavelength and the irradiation power were investigated using excimer lasers (XeCl 308 nm and XeF 351 nm) [33, 30]. The results suggested that alkane dehydrogenation (alkene formation) is a one-photon process, but carbonylation is a multi-photon process. In addition, shorter wavelengths, around 300 nm, were quite effective for carbonylation, whereas longer wavelengths were as effective as shorter for dehydrogenation.

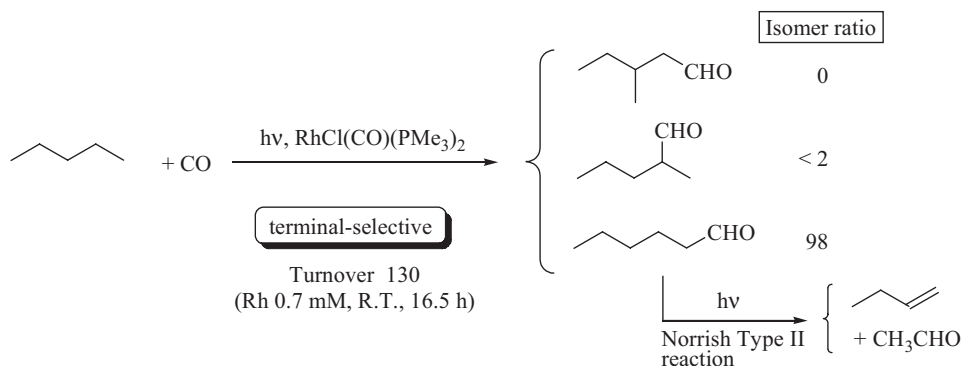
2.4.2.3 Scope and Limitations

2.4.2.3.1 Carbonylation [4]

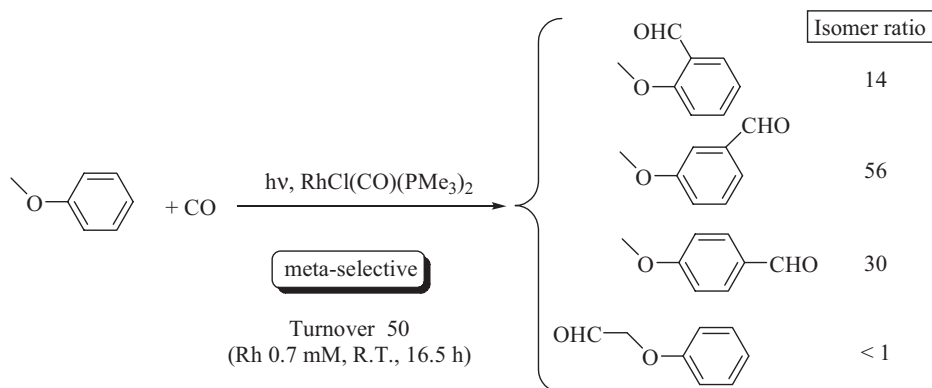
The reactions catalyzed by the $\text{RhCl}(\text{CO})(\text{PMe}_3)_2$ system can be divided into two categories, insertion and dehydrogenation (Scheme 1). Carbon monoxide, isonitrile, and acetylene are typical unsaturated compounds that insert into C–H bonds. The general characteristics of the catalytic system are seen in the carbonylation reaction (aldehyde synthesis). The most fascinating feature of the reaction is the unprecedentedly high, and unique, regioselectivity. For example, reaction of *n*-pentane with carbon monoxide exclusively yielded *n*-hexanal (Scheme 4). Prolonged reaction resulted in a secondary photoreaction of *n*-hexanal (Norrish Type II) to give 1-butene and acetaldehyde. Because the bond energy of the C–H bond increases in the order tertiary, secondary, and primary, terminal methyl groups should be the least reactive C–H bond, which is observed for radical reactions. Before our report, only enzymes could selectively functionalize methyl groups in alkanes. The $\text{RhCl}(\text{CO})(\text{PMe}_3)_2$ system also has unique regioselectivity in the carbonylation of substituted arenes (Scheme 5). For example, the carbonylation of anisole afforded *ortho*-, *meta*-, and *para*-anisaldehyde in the ratio 14:56:30. This selectivity, which is completely different from that observed in radical or electrophilic reactions, must be a characteristic of C–H oxidative addition to low-valent transition metals.

The effects of catalyst structure and wavelength are summarized as follows.

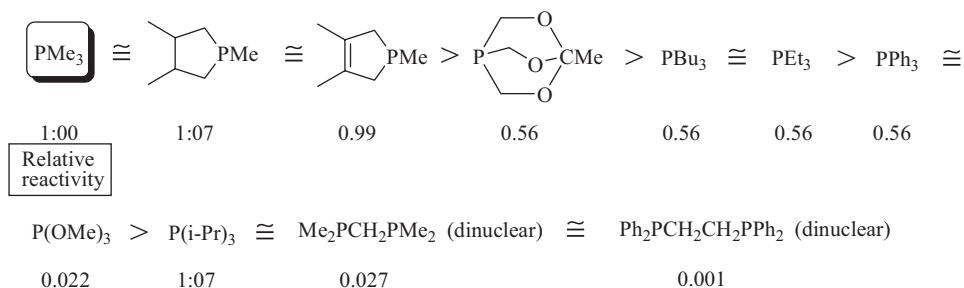
- Rhodium and chloride are the best central metal and anionic ligand, respectively; and
- Phosphine ligands are crucial for a high catalytic activity. Scheme 6 shows the relative catalytic activity of $\text{RhCl}(\text{CO})(\text{PR}_3)_2$ complexes with a variety of phosphine ligands. Promotion of oxidative addition and prevention of ligand tail biting will lead to higher catalytic activity. In other words, the ligands should be strong electron donors and resistant to intramolecular C–H oxidative addition. For example, highly electron-donating and sterically small phosphines, such as 1,3,4-trimethylphospholane and 1,3,4-trimethylphospholene, were as effective as trimethylphosphine.



Scheme 4. Carbonylation of *n*-pentane by the RhCl(CO)(PMe₃)₂ system.



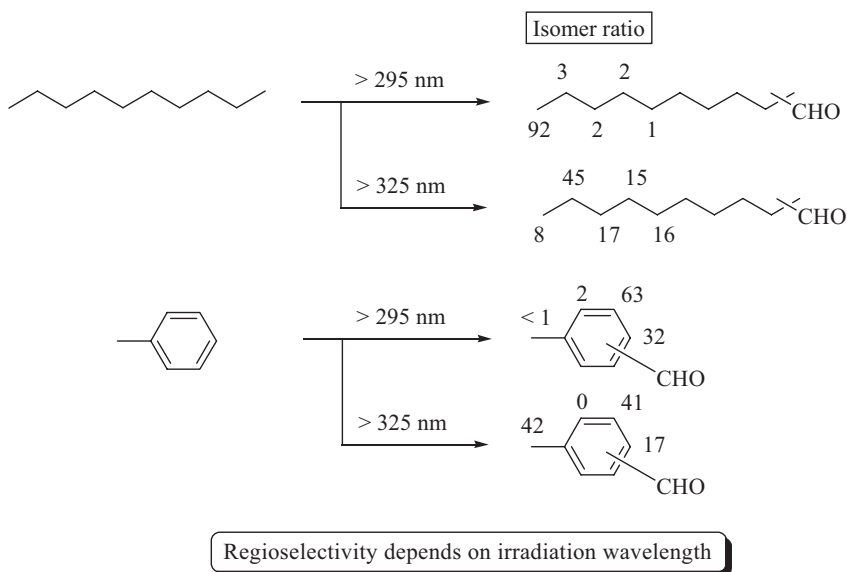
Scheme 5. Carbonylation of anisole by the RhCl(CO)(PMe₃)₂ system.



Scheme 6. Effect of phosphine ligands on the carbonylation of benzene by the RhCl(CO)(PR₃)₂ system.

- Irradiating at rather short wavelengths (approx. 300 nm) is essential for realizing the unique regioselectivity. When short wavelengths (below 325 nm) were cut off, the weakest C–H bonds were carbonylated: methylene in alkanes and benzylic methyl in toluene (Scheme 7).

In addition to carbon monoxide, other unsaturated compounds, for example isonitriles and acetylenes, can also insert into C–H bonds to give aldimines and substituted alkenes, respectively [12, 13]. Similar to carbonylation, high terminal selectivity for *n*-alkanes were also observed in these reactions.



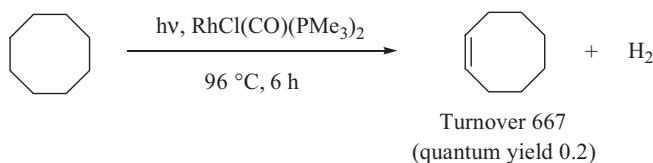
Scheme 7. Effect of wavelength on the carbonylation of *n*-decane and toluene by the $\text{RhCl}(\text{CO})(\text{PR}_3)_2$ system.

2.4.2.3.2 Dehydrogenation [14]

The other important reaction category is dehydrogenation, especially the conversion of alkanes to alkenes. The reactivity of the substrate decreases in the order cyclooctane > cyclohexane > *n*-alkane. The reaction proceeds well even under a hydrogen atmosphere. Irradiation must be the driving force for promoting the thermodynamically unfavorable reaction. Because of the increased demand for hydrogen as a clean energy, this alkane dehydrogenation is also of interest for production of hydrogen. Indeed, equimolar amounts of dihydrogen to alkenes can be detected. The dehydrogenation mechanism is β -hydride elimination from the alkyl(hydrido) intermediate (**C** in Scheme 1) then dissociation of alkenes and reductive elimination of dihydrogen. This catalytic cycle is easily understood as the reverse of alkene hydrogenation by metal complexes.

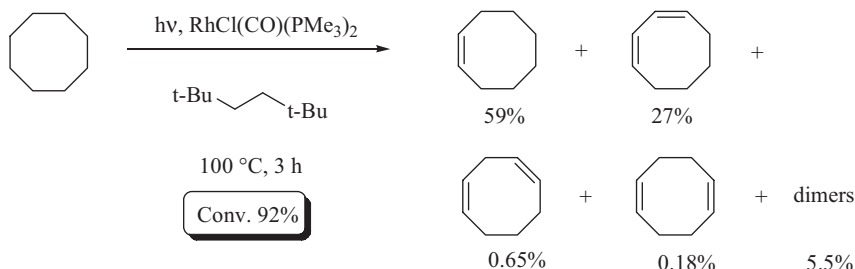
The turnover rate of the dehydrogenation of cyclooctane at room temperature is about ten times that of the carbonylation of benzene. Heating further accelerates the dehydrogenation; the quantum yield reached 0.2 at 96 °C (Scheme 8). The catalytic system has a long life; a total turnover over 1000 was readily achieved in the dehydrogenation of cyclooctane. When acyclic alkanes were dehydrogenated,

internal alkenes were obtained as the major isomers. These products partially resulted from isomerization of terminal alkenes to the thermodynamically more stable internal alkenes. Terminal alkenes could be obtained in the presence of additional phosphine ligand at the expense of the reaction rate.



Scheme 8. Dehydrogenation of cyclooctane by the $\text{RhCl}(\text{CO})(\text{PR}_3)_2$ system – high quantum yield.

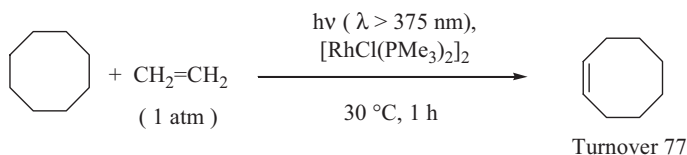
A fundamental problem of C–H bond activation with homogeneous catalysis is the lack of suitable reaction media, because typical organic solvents cannot survive under C–H bond activation conditions. Because reactions are usually conducted in neat substrates as the reaction media, conversions are limited to low levels. The reactions of gaseous substrates, for example methane, ethane, and propane are also troublesome. We have successfully achieved high conversion, over 90 %, in alkane dehydrogenation by using a very bulky alkane, for example 2,2,5,5-tetramethylhexane (Scheme 9) [17]. In the reaction of cyclooctane, as the conversion increased the initially formed cyclooctene reacted further to give 1,3-cyclooctadiene. It should be noted that diluting cyclooctane with 2,2,5,5-tetramethylhexane did not significantly reduce the initial turnover rate compared with the reaction of neat cyclooctane; this strongly suggests that oxidative addition of a C–H bond to the rhodium complex is not the rate-determining step in this dehydrogenation.



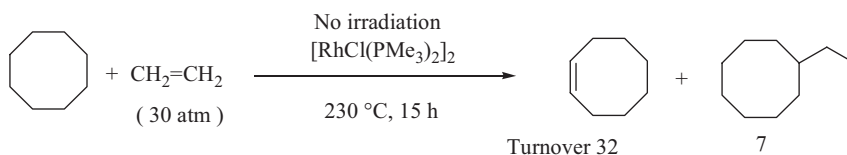
Scheme 9. Dehydrogenation of alkanes by the $\text{RhCl}(\text{CO})(\text{PMe}_3)_2$ system – achievement of high conversion.

Supercritical CO_2 has also recently attracted much attention as a reaction medium for C–H bond activation, because CO_2 is miscible with organic compounds, including organometallic compounds, and potentially stable toward alkane activation conditions. We have successfully applied supercritical CO_2 to the carbonylation and dehydrogenation of hydrocarbons [34]. The technique is effective for conversion of gaseous substrates such as methane and ethane [35].

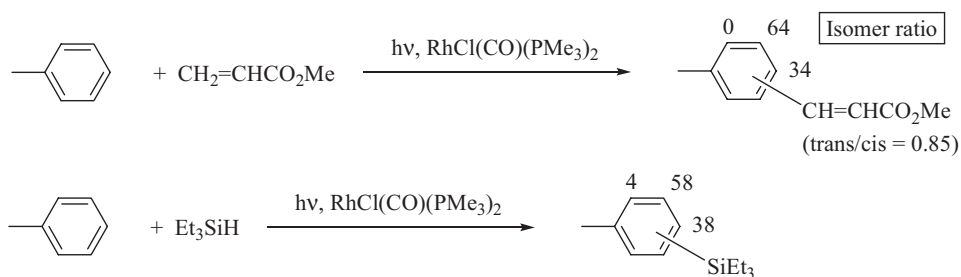
A drawback of the $\text{RhCl}(\text{CO})(\text{PMe}_3)_2$ system is the need for near-UV irradiation. Modifying the catalyst structure enabled visible light to be used. The λ_{max} of $\text{RhCl}(\text{CO})(\text{PMe}_3)_2$ appears at 365 nm whereas the ethylene analog, $\text{RhCl}(\text{CH}_2=\text{CH}_2)_n(\text{PMe}_3)_2$ ($n=1$ or 2) prepared from $(\text{RhCl}(\text{CH}_2=\text{CH}_2)_2)_2$ and PMe_3 [36], has λ_{max} in the visible region. Dehydrogenation of cyclooctane proceeds in the presence of $\text{RhCl}(\text{CH}_2=\text{CH}_2)_n(\text{PMe}_3)_2$ under an ethylene atmosphere while irradiating with visible light (Scheme 10) [20]. $\text{RhCl}(\text{CH}_2=\text{CH}_2)_n(\text{PMe}_3)_2$ also catalyzes thermal C–H bond activation. Thus, cyclooctane was converted to cyclooctene and ethylcyclooctane at elevated temperature (Scheme 11) [21]. In the Rh-catalyzed vinylation and dehydrogenative silylation of toluene under irradiation almost the same regioselectivity was observed as in the carbonylation (o:m:p=0:2:1) (Scheme 12) [23, 24].



Scheme 10. Visible light-promoted dehydrogenation of cyclooctane.



Scheme 11. Thermal C–H bond activation by the rhodium ethylene complex.



Scheme 12. Dehydrogenative vinylation and silylation of toluene.

Experimental

Synthesis of the Catalyst

$\text{RhCl}(\text{CO})(\text{PMe}_3)_2$ was prepared by a modification of the literature method [36]. Trimethylphosphine (1.7 g, 22 mmol) was added dropwise to a solution of

[RhCl(CO)₂]₂ (1940 mg, 10 mmol) in benzene (10 mL) at room temperature under nitrogen. Evolution of carbon monoxide was observed, with the formation of a yellow precipitate. After 1 h the reaction mixture was concentrated in vacuo at room temperature. The resulting yellow solid dissolved in MeOH (25 mL) was cooled very slowly to 0 °C. The large yellow prism formed was dried in vacuo to afford 2.3 g (71 %) RhCl(CO)(PMe₃)₂. Cooling of the mother liquid from the MeOH recrystallization to -50 °C gave another 0.65 g of the complex. The melting point [37, 38], IR [39], and ¹H and ³¹P NMR [38] spectra were all identical with those reported in the literature. Most of the other Vaska-type rhodium complexes were synthesized similarly.

General Procedure

A solution of RhCl(CO)(PMe₃)₂ and a reagent (carbon monoxide, isonitrile, acetylene, olefin, hydrosilane, etc.) in a hydrocarbon was irradiated with a high-pressure mercury lamp. Dehydrogenation of alkanes and dehydrogenative coupling of arenes were conducted without additional reagents under an inert atmosphere. The reactions were conducted in a Pyrex flask with an immersion-type lamp unless otherwise stated. Wavelength-regulated reactions were conducted with a lamp-housed high-pressure mercury lamp through glass filters. The products were identified by comparison of gas chromatographic (GC) retention times in capillary columns and fragmentation patterns from GC–mass spectroscopy (MS) with those of authentic samples. When authentic samples were not available, products were isolated and characterized by NMR, IR, and mass spectroscopy and elemental analysis. Yields were usually evaluated by use of capillary GC with an internal standard.

2.4.3

Stereoselective Photocyclization of Ketones (Norrish–Yang Reaction)

Pablo Wessig

2.4.3.1 Introduction and Fundamental Examples

In 1934 Norrish and Appleyard observed, on irradiation of aliphatic ketones **1** (R¹ = alkyl, X = C(sp³)), a cleavage reaction providing ketones **3**, whose alkyl chain was cleaved between the carbon atoms α and β to the carbonyl group, and alkenes **4** [1]. Nowadays, this cleavage reaction is named “Norrish-type-II cleavage”. Certainly because of limited analytical capability 70 years ago Norrish and Appleyard did not find the second group of products formed by the same initial process, i.e. cyclization products. Only Yang and Yang recognized in 1958 the formation of cyclobutanes **5** besides the Norrish-type-II cleavage products (**3**, **4**) [2]. This discovery was the basis of a very versatile and valuable ring-closure reaction that has therefore been termed the “Norrish–Yang reaction”. The occurrence of diradicals **2** as key intermediates is an important feature of this reaction (Scheme 1).

Depending on the linking group X, a variety of carbo- and heterocyclic compounds has been prepared by means of the Norrish–Yang reaction [3]. Accordingly, cyclopropanes, cyclobutanes (the Yang reaction in the narrow sense), azeti-



2

3

4



The complex reaction mechanism of the Norrish–Yang reaction has been discussed in several reviews [3]. Here, only the most important mechanistic cornerstones will be mentioned. The following aspects will be addressed:

- type of electronic excitation
- singlet vs. triplet state of ketones and resulting diradicals
- influence of the spin state on the lifetime and the ring closure of the diradicals
- hydrogen back-transfer, CT quenching, and Norrish-type-I cleavage
- reasons for regioselectivity and stereoselectivity
- memory effect of chirality

The Norrish–Yang reaction is initiated by $n\text{--}\pi^*$ excitation of the carbonyl group for which the excitation wavelength varies from 280 nm (aliphatic ketones) to 350 nm (aromatic ketones). The species formed by this excitation are characterized by strong localization of the spin density on the oxygen atom, which leads to reactivity comparable with that of alkoxy radicals. The key step of the Norrish–Yang reaction is intramolecular hydrogen migration from an sp^3 carbon atom to the oxygen atom of the carbonyl group. It should be noted that the C–H bond does not have to be activated in any way. As a result a 1, n -diradical is formed (cf. Scheme 1). At this point the spin state of the excited ketone and, consequently, of the diradical formed should be focused on. The initially formed $n\text{--}\pi^*$ excited state of the ketone is a singlet state (S_1) which can react in three ways. Besides radiationless decay to the ground state, hydrogen migration (i.e. chemical deactivation) can compete with the *intersystem crossing* (ISC) giving the triplet excited state of the ketone (T_1). The ratio of hydrogen migration from the singlet excited state to ISC depends on the nature of residue R^1 (Scheme 1). In aliphatic ketones ($R^1 = \text{alkyl}$) and 1,2-dicarbonyl compounds ($R^1 = \text{acyl}$) the ISC rate is much slower than in aromatic ketones ($R^1 = \text{aryl}$). Therefore, the products of aliphatic ketones and 1,2-dicarbonyl compounds may arise from both singlet and triplet states, whereas the products of aromatic ketones are mostly formed by a triplet pathway only (the ISC quantum yield of aromatic ketones is usually unity). The spin state of the ketone determines the spin state of the resulting diradicals, whose lifetime is crucially influenced by the spin state. Singlet diradicals usually survive a few picoseconds only [5] and should not, therefore, be regarded as true intermediates. In contrast with this, triplet diradicals, which cannot cyclize without repeated ISC, have lifetimes between 30 and 100 ns [6].

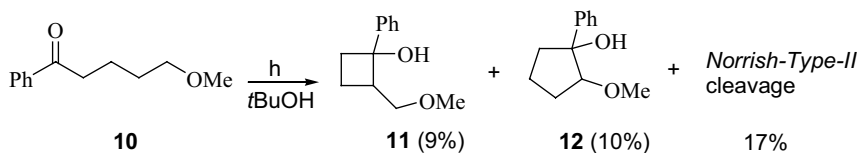
It is worthy of note that many aromatic ketones, which are particularly valuable synthetically, provide the corresponding diradicals quantitatively, i.e., up to this point of the reaction none of the excitation energy has been lost. Nevertheless, the quantum yields of product formation are often substantially smaller than unity. This “loss of excitation energy” is mainly because of hydrogen back-transfer, which regenerates the starting ketone. Unfortunately, the extent of this hydrogen back-transfer is difficult to predict for a particular molecule.

There are still two other factors influencing the reactivity of ketones in the Norrish–Yang reaction. If functional groups with a relatively low oxidation potential (amino, alkenyl or aryl groups, thioethers) are present in the reactants, the excited state may be quenched by partial or complete charge transfer from these groups to the excited carbonyl group. The effects of such processes may vary from a complete loss of reactivity to an entirely new reaction mode – cyclization reactions ini-

tiated by photoinduced electron transfer (PET). The second factor depends on the tendency of the residue R^2 (Scheme 1) to stabilize radicals (e.g. hydroxy or alkoxy groups). If such stabilization occurs, photochemical cleavage of the C–C bond between the carbonyl carbon atom and the α -carbon atom may compete with the Norrish–Yang reaction. This reaction is called Norrish-type-I cleavage.

Mechanistic remarks relating to the regioselectivity may be subdivided in three parts. The first deals with concepts within the framework of the “classic” Norrish–Yang reaction, i.e. homolytic hydrogen transfer is the basis of the reaction. In the second part the cyclization reactions based on photoinduced electron transfer (PET) will be discussed and in the third part the spin-center-shift approach is elucidated.

Owing to enthalpic (ring strain) and entropic factors γ -hydrogen abstraction by an excited carbonyl group is strongly favored compared with other positions. Although homolytic β -hydrogen abstraction is unfavorable, because of the ring strain of the corresponding cyclic transition state, $(\gamma + n)$ -hydrogen abstractions suffer from increasing entropic disadvantage. The six-membered transition state of γ -hydrogen abstraction is an optimum compromise between these two contrary factors. This situation can be partially altered if the C–H bond energy of the δ -C–H bonds (or more remote C–H bonds) is substantially decreased compared with those of the γ -C–H bonds. A classical example is the photochemical behavior of δ -methoxyvalerophenone **10**. On irradiation both cyclobutane **11** and cyclopentane **12** are formed (Scheme 3) [7].

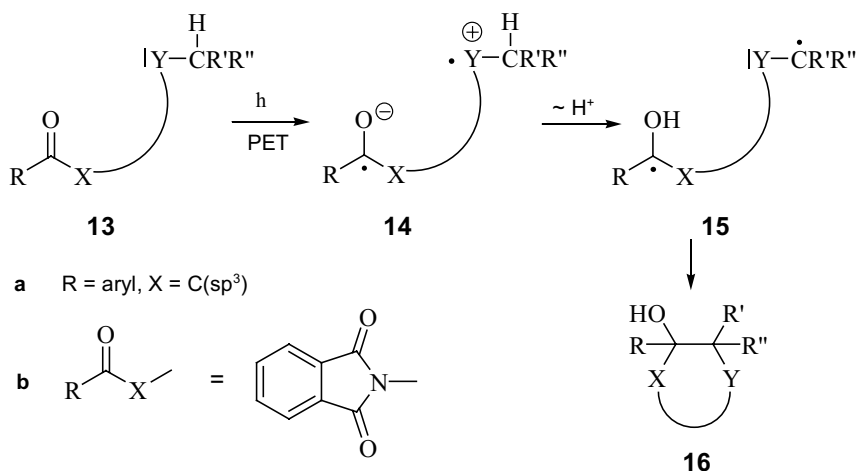


Scheme 3. Photochemical behavior of **10**.

This decrease of C–H bond energy cannot usually completely offset the preference for γ -hydrogen abstraction. A more reliable concept is based on the structural blocking of all positions between the desired $(\gamma + n)$ position and the carbonyl group, with the exception of the β -position, which needs not be blocked. Blocking means introduction of atoms or atom groups which do not bear any hydrogen atoms susceptible to the excited carbonyl group. The atoms or atom groups that fulfill this blocking function may be heteroatoms (O, N), quaternary carbon atoms, amide groups, or aromatic rings. Some examples of the application of this approach will be discussed in the next section.

Although the attempt to prevent hydrogen abstraction from a normally preferred position by introducing blocking groups is quite successful, it encounters limiting factors, especially if larger than six-membered rings must be prepared. To solve this problem one needs a process which is even faster than homolytic hydrogen transfer. This often applies to photoinduced electron transfer (PET). As mentioned above, the prerequisite for such a PET process is the presence of a

functional group with a relatively low oxidation potential, for example amine, thioether, alkene, or arene. The general mechanism is briefly depicted in Scheme 4. Initially, an electron is transferred from the group Y to the excited carbonyl group that provides the radical anion–radical cation pair **14**. It is an important characteristic feature of this step that it can occur even when a relatively large distance separates the donor group Y and the excited carbonyl group. The strong electron-withdrawing effect of the radical cation formed from Y induces increased C–H-acidity at the neighboring carbon atoms and, consequently, proton transfer results to give the biradical **15**. This proton transfer occurs mostly (but not always) from the more remote C–H position. In the last step, the biradical cyclizes to products **16** (Scheme 4).



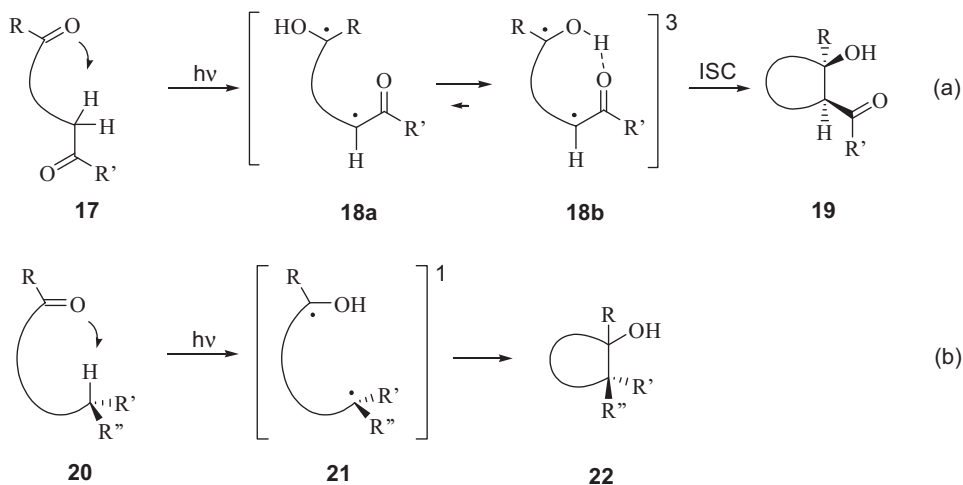
Scheme 4. Cyclization initiated by photoinduced electron transfer (PET).

Relatively few examples have been reported in which the chromophoric group was an aryl ketone (**13a**) – many more PET-induced cyclizations with phthalimides (**13b**) are known [8]. (Sometimes other imides, for example succinimides and maleimides have been used.)

All the concepts described so far have in common that the size of the initially formed biradical, i.e., the number of atoms between the radical centers, determines directly the ring size of the product. The recently developed spin-center-shift [4] substantially extends the scope of the Norrish–Yang reaction. The basic idea of this approach is to tether a leaving group X on the carbon atom adjacent to the carbonyl group (cf. Scheme 2). The most suitable leaving groups for this purpose are usually sulfonates (mesylate or tosylate) whereas phosphates, carboxylates, and carbonates may be used only in special cases (Section 2.4.3.3). On the other hand, halides, especially bromide and iodide, are unsuitable because here homolytic cleavage of the carbon–halogen bond dominates. The spin center shift is accompanied by liberation of a strong acid, which must be intercepted to avoid

thermal or photochemical decomposition of the products. *N*-Methylimidazole has been proven to be the ideal acid scavenger [4].

With regard to the stereoselectivity of the Norrish–Yang reaction, one must distinguish between simple stereoselectivity with regard to the newly formed C–C bond and asymmetric induction by stereogenic centers already present in the reactant molecule. It should be noted that it is often difficult to explain stereoselectivity phenomena in the course of a Norrish–Yang reaction by means of simple rules – extensive quantum chemical calculations have usually been necessary to clarify a certain reaction outcome. Here, two general remarks only should be made. Because ring closure of the diradicals is very exothermic, transition geometries at which ISC occur (T_1 – S_0 intersections, which correspond to transition states in ground-state chemistry) are very early in nature and, consequently, steric interactions between the radical sites are weak. Stereoselectivity based solely on steric interactions is, therefore, usually low. Otherwise, hydrogen bonds between the radical sites are substantially more effective. An application of this approach is depicted in Scheme 5a. In diradicals **18**, generated from ketones **17** on irradiation, a hydrogen bond between the hydroxy group and a carbonyl group, tethered at the upper radical center, may be formed, favoring diradical conformer **18b**. As a result of this hydrogen bond the cis-configured cyclization product **19** is selectively formed.



Scheme 5. Stereoselectivity caused by hydrogen bonds (a) and memory effect of chirality (b).

This applies to triplet diradicals only, not to singlet diradicals whose lifetimes are too short for conformational equilibration. This may be used to conserve chirality information of the reactant as depicted in Scheme 5b. Accordingly, the singlet excited carbonyl group of a ketone **20** abstracts a hydrogen atom from a chirality center whose chirality information is preserved in the planar chirality of the extremely short-lived singlet diradical **21**. On cyclization to **22** this information is

restored and, therefore, product **22** is optically active (with regard to the upper chirality center). Admittedly, the simple diastereoselectivity is usually low in these systems [9].

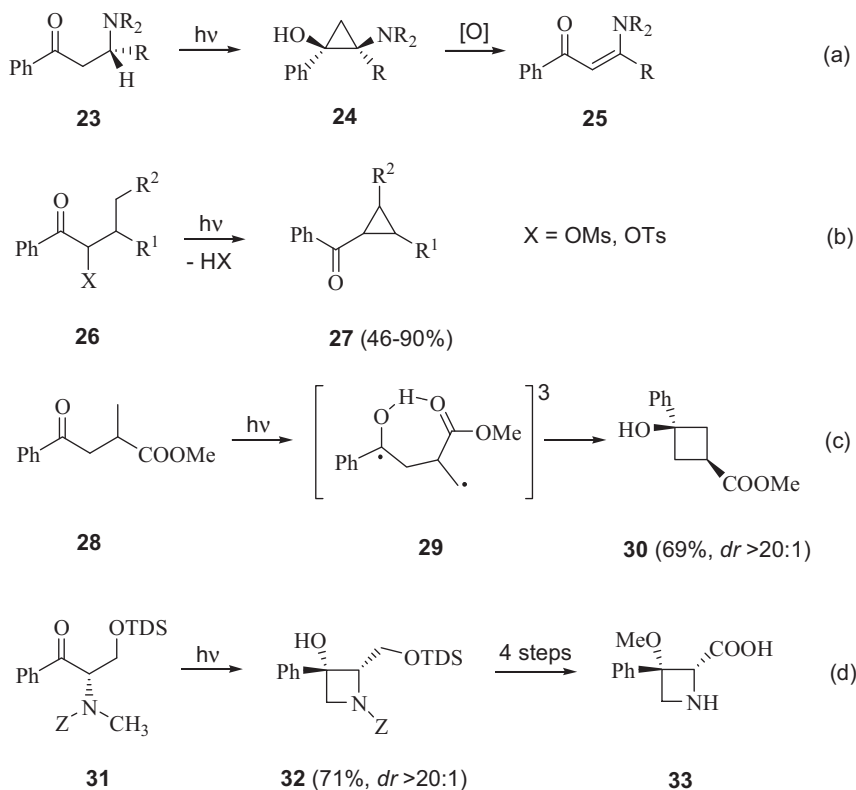
2.4.3.3 Scope and Limitations

The Norrish–Yang reaction, with the spin-center-shift extension, facilitates access to a variety of cyclic compounds. This will be discussed here, with examples of the synthesis of three- to six-membered rings; synthesis of macro- and bicyclic compounds and the photochemistry of imides will not be covered. The examples especially demonstrate the capabilities of the reaction with regard to stereoselectivity.

The formation of cyclopropanes by means of the “classic” Norrish–Yang reaction, which demands a strained five-membered cyclic transition state for the homolytic hydrogen transfer, is normally not observed. For most published cyclopropane syntheses it has either been proven or is considered very likely that the initial step is photoinduced electron transfer (PET). In addition, the hydrogen atom is not transferred homolytically, but a proton shift occurs after PET. These conditions limit the preparative scope because the electron rich functional groups responsible for the PET result in substantial sensitivity of the products to oxidative ring opening. The best investigated compounds that react in this manner are β -dialkylamino propiophenones **23**. On irradiation they cyclize to aminocyclopropanols, **24**, which are sensitive to oxygen and are, therefore, readily converted into α,β -unsaturated ketones **25** (Scheme 6a) [10]. It should be noted that the cyclization proceeds fully stereoselectively and, furthermore, if enantiomerically pure compounds **23** are used a memory effect of chirality is observed, giving enantiomerically enriched products **24** [10e].

The other way to prepare cyclopropanes is based on the spin-center-shift. Thus, aryl-alkyl ketones, **26**, bearing a leaving group X adjacent to the excited carbonyl group undergo a smooth cyclization to benzoylcyclopropanes **27** in moderate to good yields (Scheme 6b) [4a, b]. The reaction tolerates a variety of functional groups, often proceeds stereoselectively, and can be extended to the preparation of bicyclo[*n*.1.0]alkane derivatives.

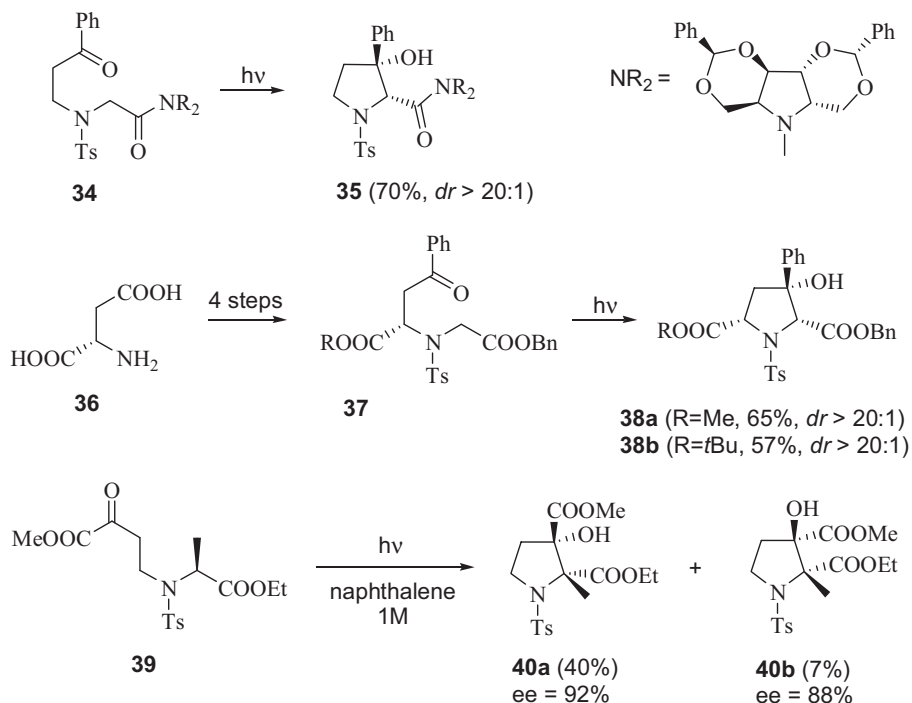
The formation of four-membered rings as the result of H-abstraction from the position γ to the excited carbonyl group is called Yang reaction. The most important drawback of this reaction is that it is usually accompanied by Norrish-type-II cleavage, already mentioned in the preceding section. This concurrent process can be restrained in two ways, both of which affect the conformation of the intermediate 1,4-diradical and, for that reason, the cleavage/cyclization ratio. The first approach is based on intramolecular hydrogen bonds, which is demonstrated with compound **28**. In the 1,4-diradical **29** an intramolecular hydrogen bond between the hydroxy group and the ester group is assumed; this both represses its cleavage and causes fully diastereoselective formation of the cyclobutane **30** (Scheme 6c) [11]. The second approach is introduction into the chain between the radical centers of a heteroatom whose conjugative interaction with one of the radical centers promotes cyclization rather than cleavage. This is exemplified by the cycli-



Scheme 6. Preparation of three- and four-membered rings.

zation of aminoketone **31** giving the azetidine **32** in good yields and, furthermore, fully diastereoselectively. Compound **32** served for the preparation of azetidine carboxylic acid **33**, a highly functionalized unnatural amino acid (Scheme 6d) [12].

The preparation of five-membered rings requires that the γ -position is blocked to enable H-abstraction from the δ -position. Whereas relatively few Norrish–Yang cyclizations furnishing carbocyclic five-membered rings have been reported, some stereoselective preparations of pyrrolidines have been reported. These reactions are based on the cyclization of protected amino acid derivatives bearing a photochemically reactive 3-oxopropyl chain on the nitrogen atom [13]. They have increased in importance as a result of use in the stereoselective preparation of proline derivatives. Scheme 7 shows three examples that follow different strategies. The glycine amide **34** contains a C_2 symmetric chiral auxiliary derived from D-mannitol. This auxiliary induces the chirality of the two newly formed stereogenic centers in the proline amide **35** ring completely selectively [14]. In contrast with this auxiliary control, the cyclization of glycine derivative **37**, prepared from aspartic acid **36**, proceeds in accordance with substrate control, i.e. the inducing chirality center is meant to remain in the product **38** [15].

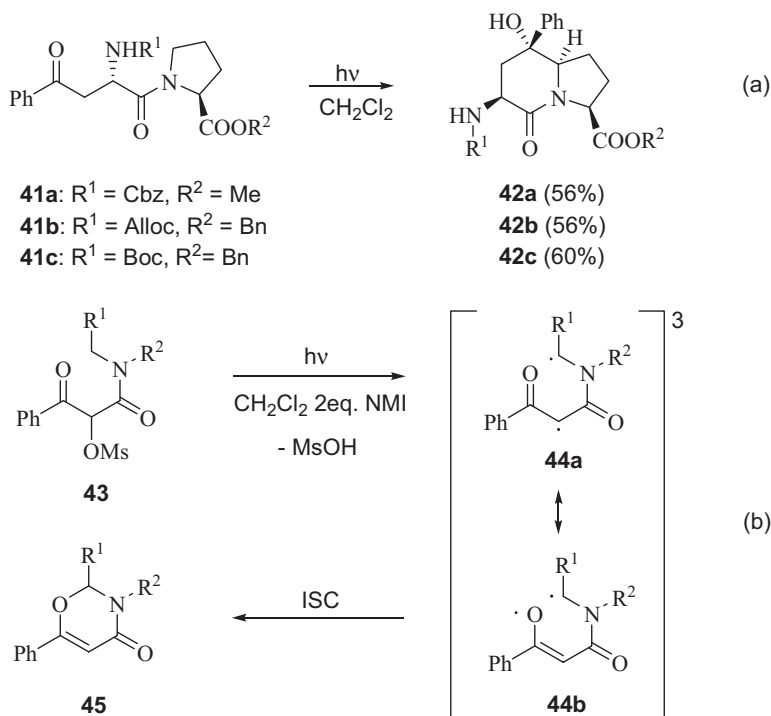


Scheme 7. Preparation of prolines.

The third example clarifies the special feature of singlet photochemistry. In contrast with **34** and **36**, the α -ketoester **39** reacts from the singlet state if irradiated in the presence of naphthalene as triplet quencher. Despite the low diastereoselectivity, the chirality of the alanine derivative **39** is completely conserved during cyclization to the pyrrolidines **40a** and **40b**. This approach has been called the *memory effect of chirality* [16].

There are relatively few examples of the preparation of six-membered rings, which require a blocking of both the γ - and δ -positions. This function may be fulfilled by an aromatic ring or by an amide group. Naphthalene derivatives have been prepared by the former approach [17]. The latter approach enables convenient access to different δ -lactams [18]. Scheme 8a shows an interesting application – the preparation of β -turn peptide mimetics [19]. Dipeptides **41**, prepared from L-benzoylalanine and L-proline, can be stereoselectively cyclized on irradiation, providing the bicyclic lactams **42** in good yields.

Another example of the application of the spin-center-shift concept is depicted in Scheme 8b. On irradiation of β -ketoamides **43**, hydrogen abstraction occurs from the δ -position, followed by smooth elimination of methanesulfonic acid. In contrast with the applications of spin-center-shift mentioned above, the enolate radical moiety of biradicals **44** reacts solely as oxygen radicals **44b** to give the oxazinones **45** [20].



Scheme 8. Preparation of six-membered rings.

Experimental

trans-1-Benzoyl-2-methyl-cyclopropane (**27**, $R^1 = \text{Me}$, $R^2 = \text{H}$, see Scheme 6)

Irradiation of α -mesyloxyisovalerophenone **26** ($R^1 = \text{Me}$, $R^2 = \text{H}$, $X = \text{OMs}$, see Scheme 6, 1.024 g, 4.0 mmol) was performed in CH_2Cl_2 (400 mL) in the presence of *N*-methylimidazole (2 equiv.) by means of a high-pressure mercury arc lamp (150 W, Hanau TQ150). Light of wavelength below 300 nm was absorbed by means of a Pyrex glass jacket between the lamp and the reaction vessel. The reaction was monitored by TLC and stopped when the reactant had completely disappeared (30–60 min). The solution was washed with H_2O ($2 \times 100 \text{ mL}$), dried over anhydrous MgSO_4 , and concentrated in vacuo to 10 % of the original volume. Silica gel (5 g) was added to the solution and the remaining solvent was removed under reduced pressure. The residue was purified immediately by FCC (petroleum ether/ethyl acetate mixtures, 100:3–100:15) to give *trans*-1-benzoyl-2-methyl-cyclopropane (576 mg, 90 %) as a colorless oil. ^1H NMR (300 MHz, CDCl_3): 8.03–7.99 (m, 2 H); 7.57–7.45 (m, 3 H); 2.45–2.38 (m, 1 H); 1.67–1.56 (m, 1 H); 1.54–1.47 (m, 1 H); 1.23 (d, 3 H, $J = 5.9$); 0.94–0.87 (m, 1 H). ^{13}C NMR (75.5 MHz, CDCl_3): 200.0 (C=O); 138.0 (aromat. Cq); 132.5, 128.4, 127.9 (aromat. CH); 26.3 (CH); 21.2 (CH); 20.0 (CH_2); 18.2 (CH_3). IR (film): 1665, 1448, 1402, 1222,

699. EI-MS: 160 (15, M^+), 105 (100, PhCO^+), 77 (49, Ph^+), 57 (19), 55 (19), 51 (19), 43 (21). Anal. calc. for $\text{C}_{11}\text{H}_{12}\text{O}$ (160.21): C: 82.46, H: 7.55; found: C: 81.78, H: 7.54.

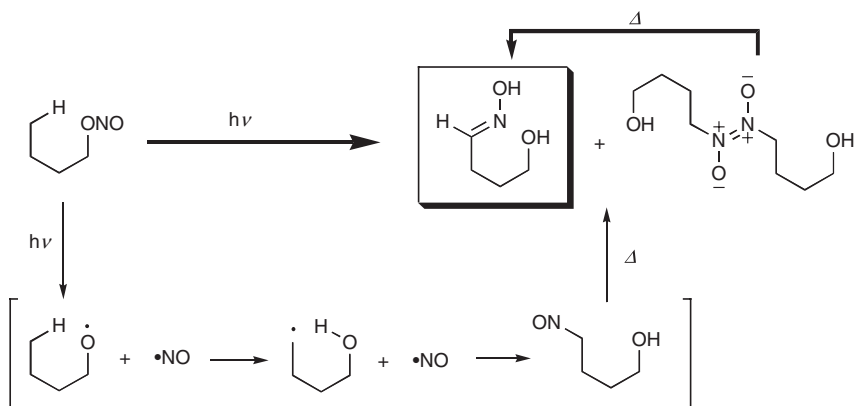
2.4.4

The Barton Reaction

Hiroshi Suginome

2.4.4.1 Introduction and Fundamental Examples

The photolysis of organic nitrites of appropriate constitution and conformation in solvents such as benzene or acetonitrile transforms them into Δ -nitroso alcohols via the sequence: (1) a homolytic fission of the O–N bond of their nitrosoxy group; (2) an intramolecular δ -hydrogen abstraction of the resulting alkoxy radicals to generate a δ -carbon radical; and (3) formation of δ -nitroso alcohols by combining of the δ -carbon radical with the generated nitric oxide. The nitroso alcohols are isolated as δ -hydroxyimino alcohols as a result of spontaneous thermal isomerization or as nitroso-dimers [1] (Scheme 1). This transformation has been named the “Barton reaction” [2, 3].

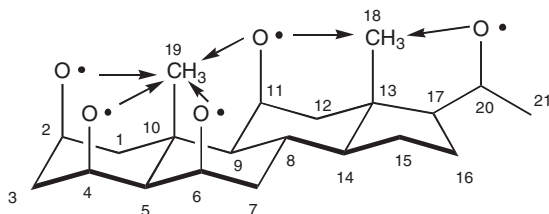


Scheme 1. The Barton reaction.

This reaction, reported in 1960, has been shown not only to be one of the most useful photochemical processes for selective functionalization of an unactivated carbon atom in organic synthesis, but has also led to general recognition of the utility of photochemical and radical reactions in organic synthesis.

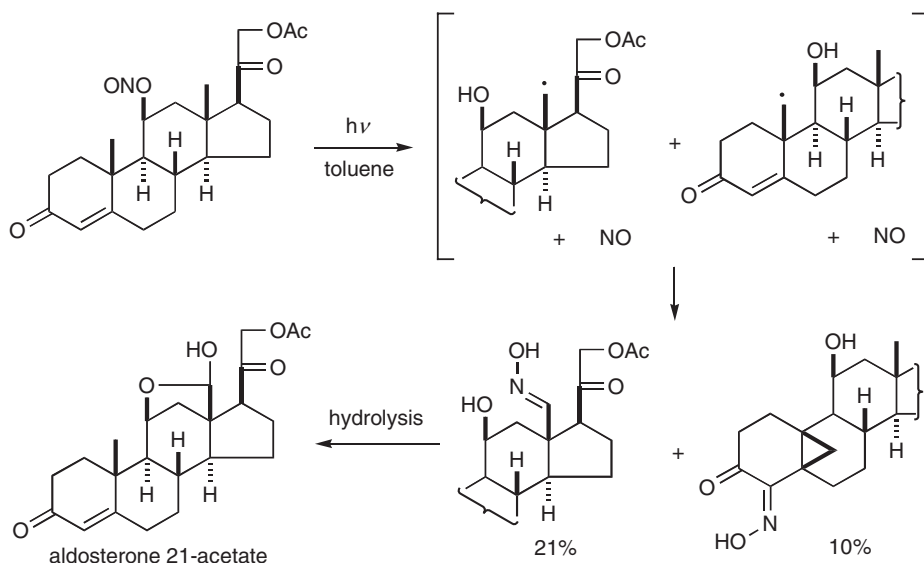
Several experiments with a variety of cyclic and acyclic molecules have established that hydrogen abstraction involving a 6-membered cyclic transition state is preferred over those involving 5- or 7- (and more) membered cyclic transition states. Because angular methyl groups and alkoxy radicals with a 1,3-diaxial relationship in rigid steroid and some terpenoid molecules ideally satisfy hydrogen abstraction through a 6-membered cyclic transition state, the Barton reaction has most successfully been applied to the field of steroids and some di- and triterpe-

noids. By this reaction, functional groups can, in principle, be introduced into the unactivated angular 10β - or 13β - methyl groups of steroids. As shown in Scheme 2, a hydrogen attached to the 13β -carbon can be abstracted by an alkoxy radical attached to C11, C15, or C20, and a hydrogen attached to the 10β -carbon by an alkoxy radical at C2, C4, C6, or C11. Thus one-step introduction of functionality into an unactivated CH can be achieved.



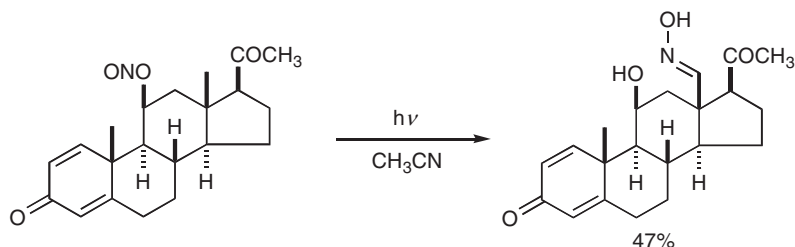
Scheme 2. Remote functionalization of steroids by the Barton reaction.

Among the numerous applications of this reaction reported over four decades, some typical examples of the functionalization are outlined in Schemes 3 to 10. Thus, Scheme 3 outlines the well-known Barton transformation of corticosterone acetate nitrite into aldosterone acetate oxime which, with nitrous acid, gives aldosterone 12-acetate [4]. The yield of 18-oxime is, however, rather low (21%), since attack by the 11β -alkoxy radical on C-19 competes with the desired attack on C-18. Incorporation of the 1,2-double bond into the nitrite prevented undesired C-19 attack by the radical and a far better yield (47%) of 18-oxime was achieved [5] (Scheme 4). This example may indicate that the Barton reaction is sensitive to



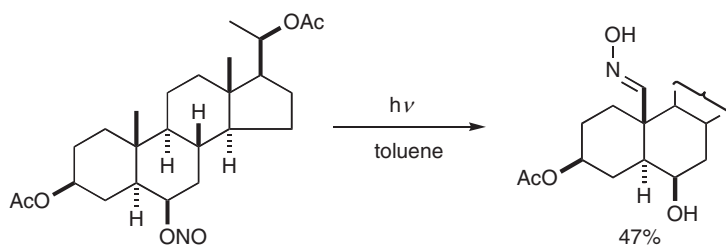
Scheme 3. Transformation of corticosterone acetate nitrite into aldosterone 21-acetate.

structural changes, and that the distance and conformation requirements between the alkoxy radical and the methyl group, which are in a 1,3-diaxial relationship, are rather strict.

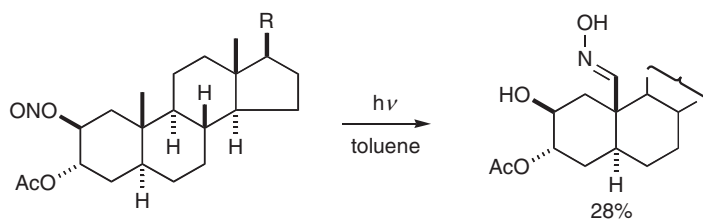


Scheme 4. Functionalization of 13 β -Me in a 1,2-dehydrosteroid.

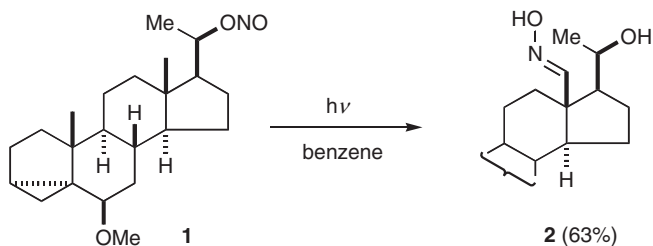
Schemes 5 and 6 outline the functionalization of a 10 β -Me by a steroidal 6 β -ol [1] and a 2 β -ol nitrite [6]. Functionalization of 13 β -Me by a 20 α -ol nitrite [7] and functionalization in the terpenoid field [8] are outlined in Schemes 7 and 8. The last example involves a 7-membered cyclic transition state that seldom occurs. Scheme 9 outlines a recent application of the Barton reaction in the synthesis of a biologically active carbacepham [9]. The photolysis of acyclic 5-phenyl-1-pentanol nitrite gives, preferentially, a nitroso dimer arising as a result of the abstraction of a hydrogen attached to the δ -carbon, rather than the ϵ -carbon from which the better stabilized benzyl radical can be generated (Scheme 10) [10].



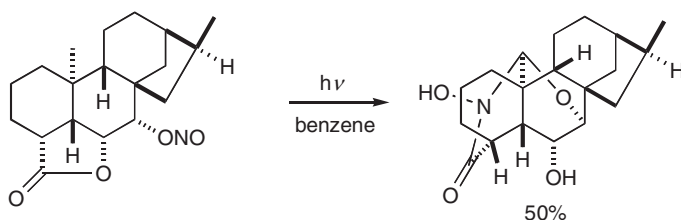
Scheme 5. Functionalization of the 10 β -Me of a steroid.



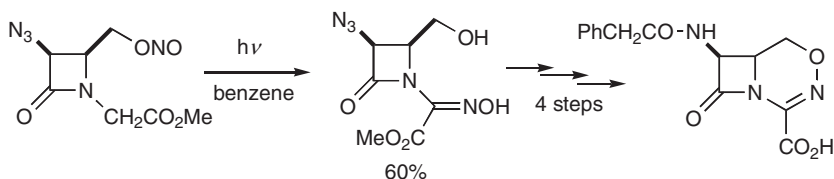
Scheme 6. Functionalization of the 10 β -Me of a steroid.



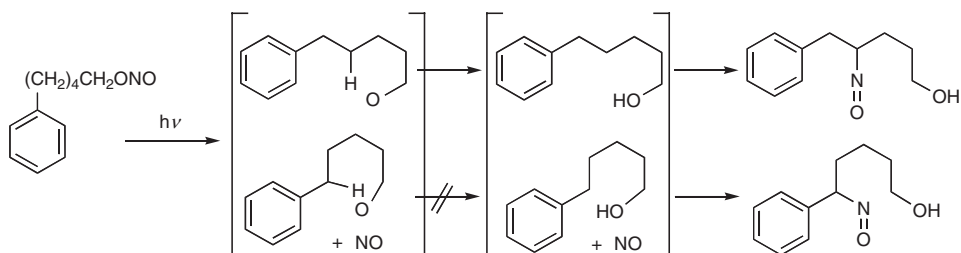
Scheme 7. Functionalization of the 13 β -Me of a steroid.



Scheme 8. Functionalization of a terpenoid.



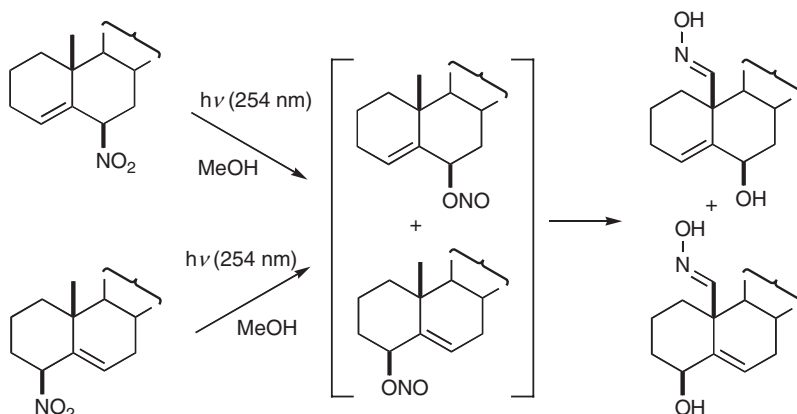
Scheme 9. Synthesis of carbacepham.



Scheme 10. Preference for δ -hydrogen abstraction in acyclic molecules.

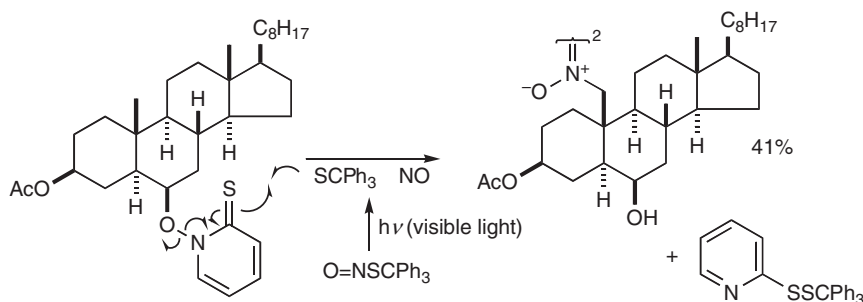
A tandem remote functionalization by an excited nitro group, which involves a photochemical nitro–nitrosoxy rearrangement followed by the Barton reaction, is outlined in Scheme 11 [11]. Thus, the photolysis of 6 β -nitrocholest-4-ene in methanol by 254 nm light gave 19-hydroxyiminocholest-4-ene 6 β -ol and its 5-ene 4 β -ol

isomer. The isomeric 4 β -nitrocholest-5-ene reacted in a completely analogous manner. The reaction involves homolysis of C–N, recombination of the NO₂ generated, to give the nitrite, and then the Barton reaction.



Scheme 11. Barton reaction involving nitro–nitrosoxy rearrangement.

Potier, Motherwell and colleagues [12] recently devised a new version of the Barton reaction in which functionalization can be achieved by irradiating a solution with visible light instead of ultraviolet light. The method employs O-alkylthiohydroxamates, which have also been proved to be efficient precursors for generation of alkoxyl radicals. Thus, irradiation of 6 β -O-acylthiohydroxamate in benzene containing equimolecular thionitrite as a donor of NO with a 250-W tungsten lamp gave the nitroso dimer (41 %) corresponding to the product obtainable by the photolysis of 6 β -ol nitrite (Scheme 12).



Scheme 12. New version of the Barton reaction.

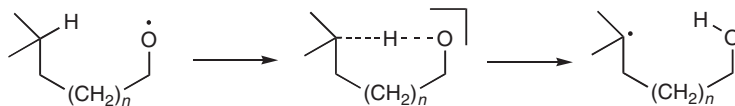
2.4.4.2 Mechanism

Alkyl nitrites, which are readily prepared by reaction of the corresponding alcohols with nitrosyl chloride in pyridine, absorb UV in two regions – a broad band centered at ca. 210 nm (ϵ 1000–1700) and a structured band at ca. 360–380 nm

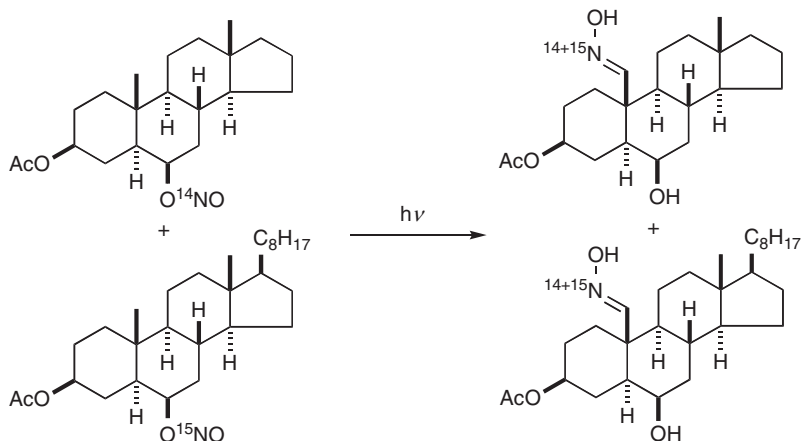
(ϵ ca. 80) [13, 14]. The absorption at the longer wavelength (S1) is assigned to the (n, π^*) transition; that at the shorter wavelength (S2) is assigned to a π, π^* transition [13], and possibly higher excited states. Irradiation of the weak n, π^* band causes homolysis of the O–NO bond to give the corresponding alkoxyl radicals and nitric oxide with a quantum yield 0.7, as has been proven by photolysis of steroidal nitrite esters in methanol with 365 nm monochromatic light [14]. A quantum yield of 0.76 has also been reported for the photolysis of acyclic octyl nitrite in heptane [15]. A quantum yield of less than unity in the solution photolysis of the nitrites may indicate the reversibility of the primary process of the dissociation.

The alkoxyl radicals thus generated abstract, intramolecularly, a hydrogen that is appropriately located. On the basis of several results in the steroid field and an inspection of the Dreiding model, the most appropriate distances between an O-radical and a carbon bearing a hydrogen atom to be abstracted have been estimated to be in the 2.5–2.7 Å range [16]. Calculations and experimental evidence relating to homolytic intramolecular 1,5 and 1,6 hydrogen transfer have indicated that the activation energy of the transfer is minimal when the C–H...O can achieve a linear transition state (Scheme 13) and that the difference in the activation energies for hydrogen transfer via 6- and 7-membered cyclic transition states is not great. The strong preference for hydrogen transfer via a 6-membered transition state is almost certainly attributable to the entropy factor.

The carbon-centered radicals thus generated then combine with nitric oxide to form nitroso compounds, which readily isomerize to afford the corresponding

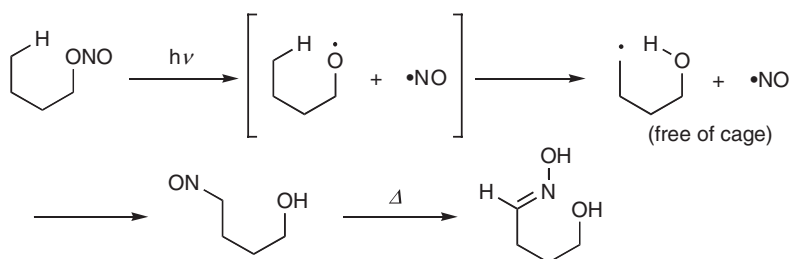


Scheme 13. Hydrogen transfer via a linear transition state ($n = 1$ or 2).



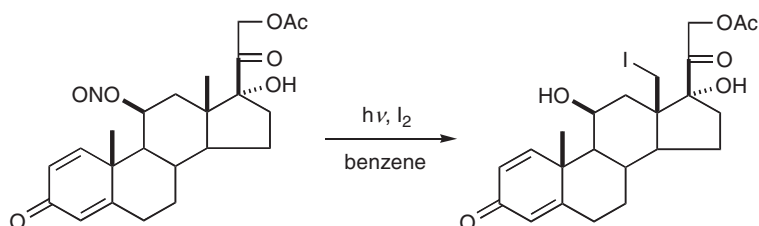
Scheme 14. ^{14}N and ^{15}N -scrambling in the photolysis of nitrites.

oximes (or nitroso dimers). Quantum-yield studies of the overall process cited above have indicated that this free-radical reaction is not a chain process. The behavior of the nitric oxide generated in the solution was studied by using labeled nitrites [17, 18]; the photolysis of a mixture of each equimolecule of ^{15}N nitrite A and ^{14}N nitrite B gave a mixture of two products (arising from intramolecular hydrogen abstraction) in which ^{15}N and ^{14}N were completely scrambled in the two products (Scheme 14). It was thus concluded there is no structure keeping the NO in a solvent cage throughout the process. A similar mass-spectrometric determination on the nitrite recovered after partial completion of the photolysis showed that no scrambling occurred at this stage. These experiments indicated that non-cage combinations occur after hydrogen abstraction, although the primary homolysis step is a cage process, as outlined in Scheme 15.



Scheme 15. Non-cage combination of nitric oxide.

The formation of 18-iodopredonisolone 21-acetate, but not the corresponding 18-oxime, by photolysis of predonisolone 21-acetate nitrite in the presence of iodine in benzene is in agreement with this mechanism (Scheme 16) [19].

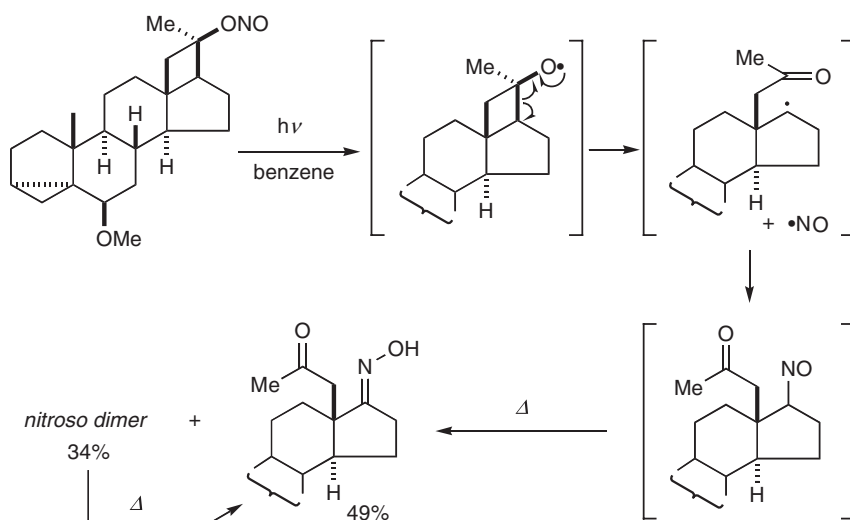


Scheme 16. Non-cage combination of iodine in the Barton reaction.

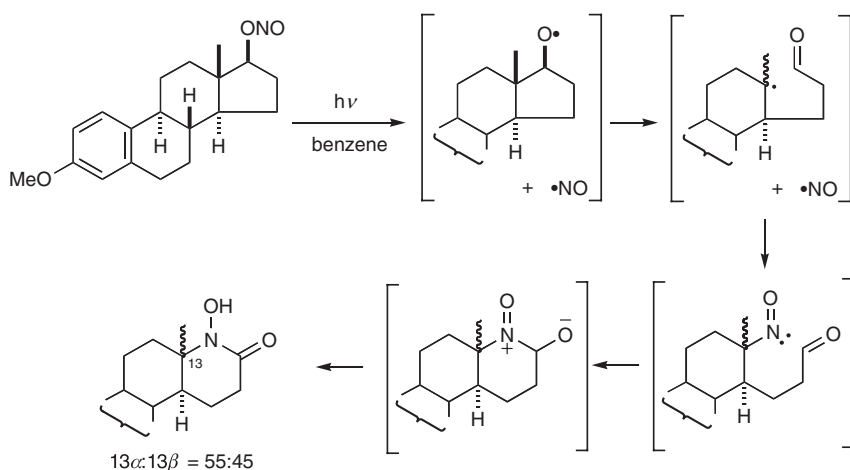
2.4.4.3 Scope and Limitations

When the alkoxy radical and the hydrogen to be abstracted are not properly disposed for the Barton reaction, the reactions of the alkoxy radical, for example β -fragmentation, intramolecular addition to the double bond, disproportionation or α -hydrogen fission, and intermolecular hydrogen abstraction, compete with the Barton reaction or result in an exclusive reaction. Among these reactions, β -frag-

mentation is frequently predominant and occurs especially readily when the cleavage relieves some strain, for example in cyclobutanoxyl radicals, or provides stabilized carbon-centered radicals, for example those conjugated with a heteroatom or with tertiary and allyl radicals. Schemes 17 to 21 [20–25] outline some typical examples in which nitrite photolysis leads to selective β -fragmentations of cyclobutanoxyl [18], cyclopentanoxyl radicals [19, 20] and α -silyl alkoxy radicals [21] to give each single product, including a novel formation of heterocyclic molecules. Although little attention was attracted to its potential in synthesis until the 1970s,

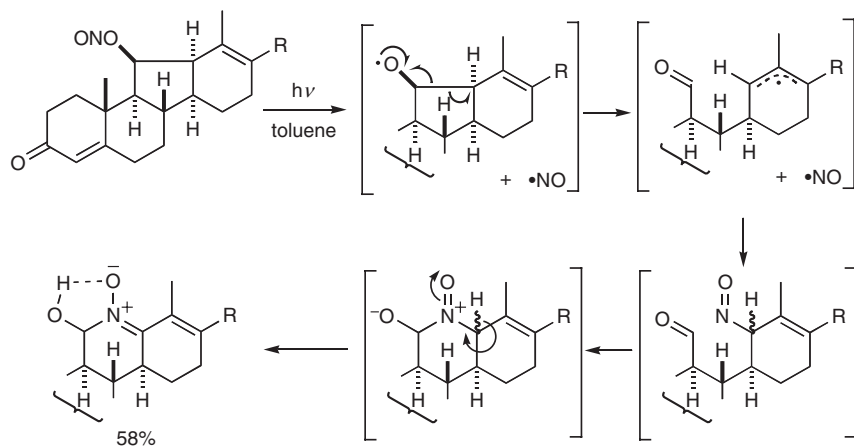


Scheme 17. β -Fragmentation in the photolysis of cyclobutanol nitrite.

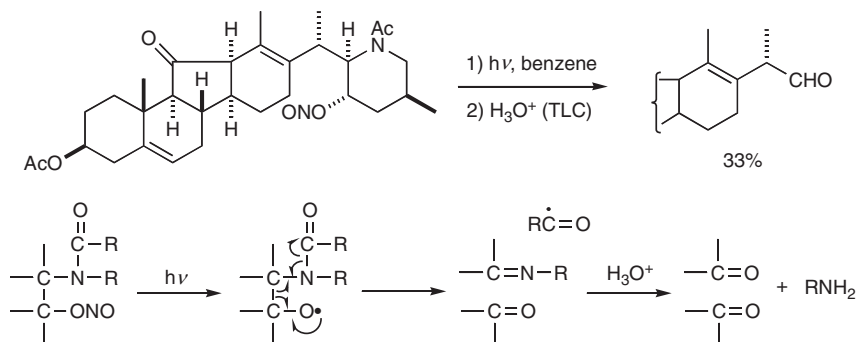


Scheme 18. Formation of a N -hydroxyamide.

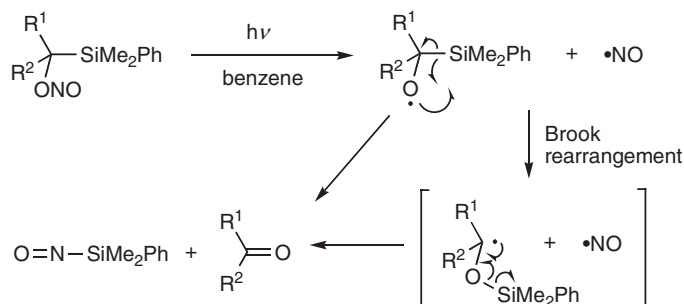
we recognized that the β -fragmentation of alkoxy radicals is as useful as intramolecular hydrogen abstraction in organic synthesis, because it occurs highly selectively [3, 20]. We have shown the usefulness of the reaction by synthesizing a variety of natural products using β -cleavage of alkoxy radicals (generated from alkyl hypiodites) as the key step. This topic has recently been extensively reviewed [20].



Scheme 19. Formation of a nitrone in nitrite photolysis.

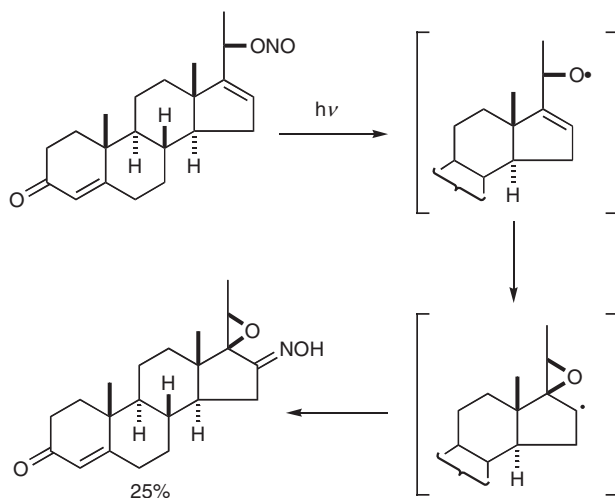


Scheme 20. Preference for β -Fragmentation in nitrite photolysis.

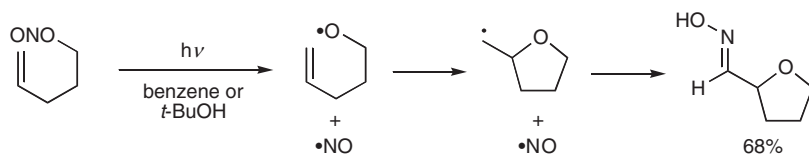


Scheme 21. β -Fragmentation in α -silyl nitrite photolysis.

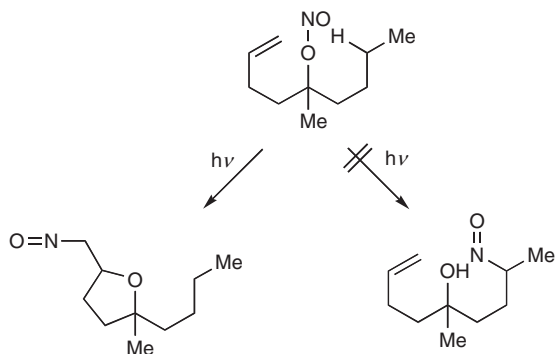
When the C-C double bond is located in a position appropriate for addition of alkoxy radicals generated from nitrites, intramolecular addition of the alkoxy radicals to the double bond occurs to give oxygen heterocycles. Schemes 22 and 23 outline examples of the formation of an epoxide [26] and a furan ring [27, 28]. As outlined in Scheme 24, formation of a 5-membered ring is preferred over a 6-membered ring in the photolysis of 1-methyl-1-butyl-4-penten-1-ol nitrite, analogous to carbon radicals. Intramolecular addition is preferred in a molecule that is capable of undergoing both cyclic addition and the Barton reaction, as outlined [28].



Scheme 22. Formation of an oxirane.

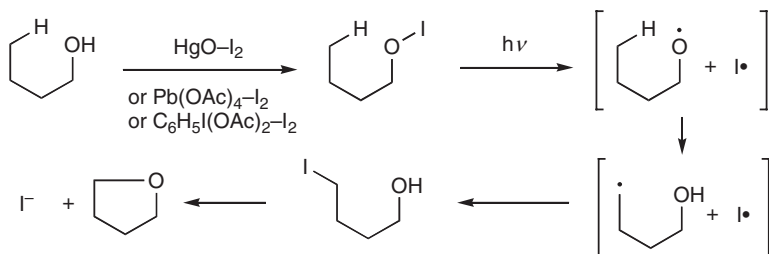


Scheme 23. Formation of a furan ring.



Scheme 24. Preference for alkoxy radical addition in nitrite photolysis.

The photolysis of alkyl hypohalites, especially alkyl hypoiodites [29], can be used in a manner similar to the organic nitrites for functionalization of an unactivated carbon atom. Scheme 25 outlines a general scheme for remote functionalization by the hypoiodite reaction. Readers requiring more information on this subject are advised to refer to review articles [2c, 16, 20].



Scheme 25. Functionalization of unactivated CH by photolysis of hypoiodite.

Experimental

18-Hydroxyimino-6 β -methoxy-3 α ,5-cyclo-5 α -pregnan-20 α -ol (2 in Scheme 7) by photolysis of 6 β -methoxy-3 α -5-cyclo-5 α -pregnan-20 α -ol nitrite (1 in Scheme 7)

A solution of nitrosyl chloride in pyridine was added dropwise to a solution of 258 mg (0.777 mmol) pregnan-20 α -ol in pyridine until the solution turned brown. The solution was stirred for 3 min at room temperature and then poured into a mixture of water and ice. The crystals, collected by filtration, were dissolved in diethyl ether. The solution was worked up in the usual way. Evaporation of the solvent gave nitrite **1**, which was dissolved in a mixture of 20 mL each of benzene and methanol. The solution in a Pyrex tube was irradiated with a 100-W high-pressure Hg arc lamp for 1 h at room temperature. The solvent was then removed and the product subjected to TLC (silica, hexane–ethyl acetate, 1:1) which revealed the presence of three products. The most mobile fraction in TLC was the parent ketone (26 mg, 10%). The next most mobile product was pregnan 20 α -ol (16 mg, 4%). The most polar product was the 18-hydroxyiminopregnan-20 α -ol **2** (178 mg, 63%), m.p. 155–156 °C (from hexane–dichloromethane). ^1H NMR (CDCl_3 , 270 MHz) δ = 1.00 (s, 3H, 19- H_3), 1.20 (d, 3H, J = 2.57, 6 β -OMe), 3.32 (s, 3H, OMe), 4.03 (m, 1H, 20 β -H), 7.56 (s, 1H, CH=N–).

2.5

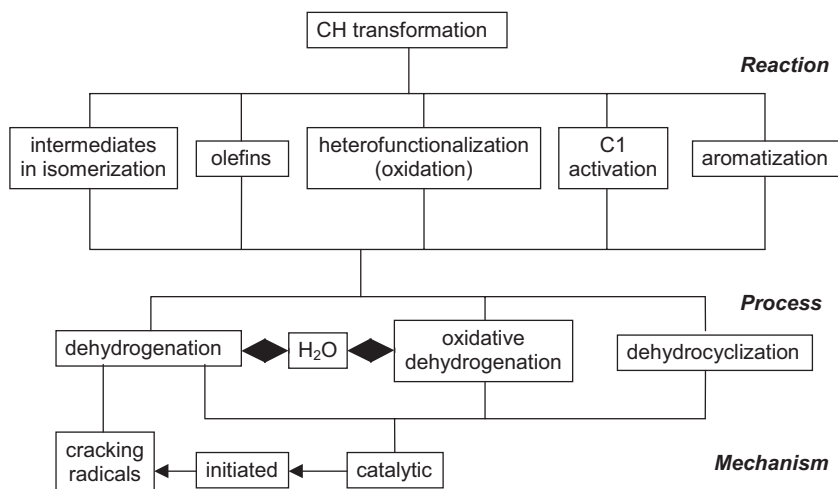
Heterogeneous Catalysts for the C–H Transformation of Unfunctionalized Alkanes

Robert Schlögl

Unfunctionalized alkanes are a major feedstock for large-scale synthesis of intermediates and monomers in the chemical industry. They occur as mixtures in natural gas and are produced by cracking of light or heavy oil fractions. Higher al-

kanes are synthesized further in the Fischer–Tropsch processes. The common molecules understood to be the “unfunctionalized alkanes” are methane, ethane, propane, the butanes, hexane and the C_{10} to C_{14} alkane fraction. Methane cannot be C–H transformed under technologically relevant conditions. It is converted into synthesis gas in the steam reforming process.

Scheme 1 summarizes the characteristics of the reactions, processes, and mechanistic aspects of this group of important chemical transformations, which form the basis of a large fraction of the current chemical industry. The reactions can be classified as intentional C–H transformations, carried out in aromatization reactions and in olefin synthesis, or as unintentional C–H transformations, for example isomerization reactions and all heteroatom functionalization such as oxidation or amination.



Scheme 1. Compilation of reactions and processes occurring during C–H transformation of small unfunctionalized alkane molecules

The activation of methane [1] is also included as one of the most desired yet not technically viable reactions. Abundant amounts of methane occur with crude oil and as gas in remote locations; it is also produced in large quantities during hydrocarbon processing. A large fraction of this methane is flared, because economical use or transportation is not possible. This gas and the abundant resources of methane gas hydrates would make a very suitable feedstock for higher hydrocarbons, if its activation to produce molecules other than synthesis gas were feasible. Despite enormous fundamental and practical efforts [1–5], no applicable method has yet been found for creation of ethylene, methanol, or formaldehyde from methane.

The use of natural gas [5–8] via synthesis gas to create higher hydrocarbon feedstock is currently being exploited in the first large plants; some characteristics are reported in Table 1. It is obvious that without highly effective catalytic systems

such complex transformations would be impossible. Heterogeneous catalysis is of strategic relevance to further exploitation of such natural resources for generation of feedstock. The overall process produces, simultaneously, high-quality transportation fuels and feedstock for the chemical industry. Its economics rely on the large scale of C–H transformation of the natural gas mixture. The demand for C₂ and C₃ feedstock is apparent from production figures for 2000 which show worldwide use of 100 million tons C₂ and 53.5 million tons C₃. A usage profile for C₃ is given in Table 2.

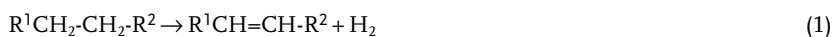
Table 1. Characteristics of a modern plant (2004) for natural gas conversion.

Feed product	Consumption/production capacity	Catalyst system used
Natural gas	$3.8 \times 10^6 \text{ m}^3 \text{ day}^{-1}$	–
Synthesis gas	$12.3 \times 10^6 \text{ m}^3 \text{ day}^{-1}$	Nickel/alumina
Methanol	$1.7 \times 10^6 \text{ m}^3 \text{ day}^{-1}$	Copper/zinc/alumina
Propene	$5.19 \times 10^5 \text{ t year}^{-1}$	Zeolithic systems
Gasoline	$1.50 \times 10^5 \text{ t year}^{-1}$	Zeolites
LPG	$3.9 \times 10^4 \text{ t year}^{-1}$	Solid acid systems

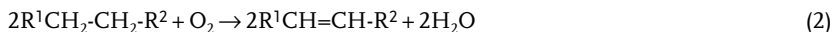
Table 2. Usage profile for propene. The figures are based on global consumption in 2000. Annual growth rates are approximately 5 % per year. 100 % is 53.5×10^6 tons

Product	Fractional consumption (%)
Polypropylene	59
Acrylonitrile	10
Poly alcohols	8
Propylene oxide	7
Cumene	6
Acrylic acid	4
Others	7

The reactions in Scheme 1 are achieved by three processes – dehydrogenation, oxidative dehydrogenation, and dehydrocyclization.



Dehydrogenation (DH) processes (Eq. 1) are always endothermic, and require high reaction temperatures and a high dilution of the organic reactants. Equilibrium conversion for these processes is well below full conversion under conditions in which selectivity above 90 % can be achieved. The fierce reaction conditions lead to massive problems with soot formation. The practical solution is often the operation of such processes with a large excess of steam providing dilution of reagents and of hydrogen to shift the equilibrium to the product side; it also accomplishes transport of energy and in-situ regeneration of spent catalysts by soot gasification.



Oxidative dehydrogenation (ODH) is an exothermic process (Eq. 2) and is not limited by an equilibrium at finite conversions. It is less demanding of reaction temperature but requires extensive heat management to avoid hot spots and runaway reactions. The reactant-oxygen mixture is rather limited in composition because of multiple explosion limits. The great challenge of designing such processes is achievement of finite selectivity to partial oxidation and suppression of total oxidation. This is expressed in Eq. (2), which shows that excess organic reactant is required to absorb the dissociation product of one oxygen molecule. It is obvious that oxidants providing only one oxygen atom per molecule, for example N_2O can greatly enhance the selectivity of such processes. It is understood in the context of this text that the oxidant for hydrogen is always dioxygen from air or from pure oxygen.

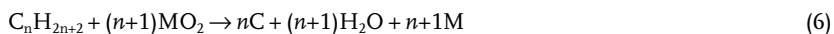


Dehydrocyclization is special case of a dehydrogenation reaction occurring at the two end carbon atoms of a chain molecule in simultaneous fashion. The process is also strongly endothermic and requires very careful control of the tendency to form soot, because this is much more energetically favored than synthesis of small aromatic molecules. The significant stabilization of the aromatic product relative to polyolefinic products is a strong driving force of the cooperative reaction and prevents significant occurrence of side reactions such as hydrogenolysis being the prominent processes with medium or long hydrocarbons during their activation. Here surface science studies are currently revealing the complex interactions at surfaces that restructure compounds during reactions and are partly covered with relevant carbonaceous deposits [9, 10].

Mechanistically it is often difficult to know if a reaction occurs by dehydrogenation or by oxide hydrogenation processes, because there are facile consecutive reactions either to form water from hydrogen initially generated from dehydrogenation (exothermic) and from oxygen from the catalyst or to form hydrogen from splitting water (endothermic) initially formed in oxidative dehydrogenation.



The net reaction energy thus provides little clue about which reaction and or consecutive coupling process occurs under practical reaction conditions. Because excess water is usually present as feed and the total oxidation of reactants (Eq. 5) and deactivation of oxidic catalysts (idealized MO_2) during coking (Eq. 6) always produce additional water, render mechanistic analysis even more difficult.



At the level of reaction mechanisms these processes occur either as homogeneous reactions under conditions of “pyrolysis” or heterogeneously in the presence of a catalyst. The catalyst can have one or several of the following functions:

1. direct activation of a C–H bond via strong Brønsted acidity (proton donor)
2. direct activation of a C–H bond via a strong base ($\text{M}=\text{O}$ group)
3. direct activation of a C–H bond via a strong Lewis acid (metal or halide)
4. stabilization of a reactive intermediate after C–H abstraction (metal–carbon bond)
5. provision of multiple reaction sites in close proximity (dehydrocyclization)
6. shift of equilibrium conversion by consecutive removal of hydrogen (water formation)

A particular function of a catalyst can be initiation of radicals desorbing from the catalyst into the gas phase where they act as homogeneous catalysts in chain reactions. Such a mechanism is very likely to operate in methane coupling at high temperatures with basic oxide catalysts (No. 2) acting on methane molecules leading to methyl radicals that start chain reactions in the gas phase [11].

The mode of operation of homogeneous or heterogeneously initiated reactions cannot be excluded in all processes under discussion. The reaction temperatures are typically between 623 K and 873 K, well within the range of pyrolysis temperatures [12]. There is ample evidence of complex and selective homogeneous reactions of unfunctionalized hydrocarbon molecules in flame chemistry [13–15].

Scheme 1 illustrates that it is by no means facile to select or design a catalyst for a desired process leading to a target reaction. Several processes are very likely to co-exist and to control the overall net reaction in a convoluted way. It is thus of little surprise there are no design rules for selection of catalysts. It is also clear that the reactions observed are strongly influenced by the macrokinetic boundary conditions. It does matter in which reaction apparatus a reaction is conducted out – the same reaction may follow different reaction mechanisms in different apparatus.

It will be always desirable to conduct C–H transformations under catalytic control to minimize the energy required and to maximize the selectivity of the reaction. Controlling the selectivity [16] is of paramount importance, because energy boundary conditions for all C–H transformations of simple alkane molecules are unfavorable. Table 3 reports, as a qualitative measure, heat of formation data

under standard conditions from the elements in their standard states. The data were calculated using the semi-empirical AM1 formalism and are accurate enough to enable meaningful comparison. The incremental energies are plotted in Figure 1.

Table 3. Energy data for small alkane molecules.
Heats of formation in kJ mol^{-1}

Molecule	Per mole	Per C atom	Per C–H unit
Methane	–36.77	–36.77	–9.20
Ethane	–72.97	–36.49	–12.16
Ethene	+68.78	+34.39	+17.20
Propane	–101.67	–33.89	–12.71
Propene	+27.32	+9.11	+4.55
<i>n</i> -Butane	–130.42	–32.60	–13.04
<i>i</i> -Butane	+18.55	+4.64	+1.85
1-Butene	+0.46	+0.10	+0.01
C_6H_{12}	–161.13	–26.85	–13.42
C_6H_6	+91.83	+15.31	+15.31
CO_2	–334.13	–	–

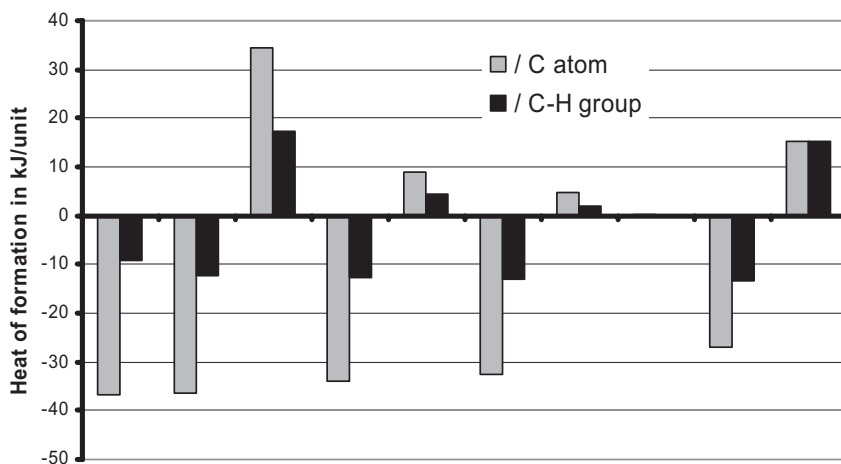


Figure 1. Energetics of small alkane molecules. Increments are shown per skeletal carbon atom and, for comparison, per C–H group in the molecule

It is clearly apparent that reactant alkane molecules are all very stable, with stability being highest for methane and decreasing gradually with increasing molecular size. The goal of C–H transformation is now to selectively activate one or few C–H bonds without activating the C–C bond system. In reactions covered by this article the resulting product molecules are olefins or aromatic compounds. All these molecules are unstable relative to the precursors and also relative to their disintegration into the elements. A large drop of the instability is observed with increasing molecule size. The aromaticity of benzene does not compensate for the stabilization of C₆ by full hydrogenation (cyclohexane).

These data imply that kinetic barriers must exist in the interaction between catalyst and organic species that are not reflected in the ground state energy data presented. Otherwise there would be little hope of achieving any C–H transformation selectively either in the absence of oxygen (preferred reaction is element formation) or in the presence of oxygen (preferred reaction is total combustion).

The catalyst must therefore activate the stable C–H without acting further on the residual C–H of the product [17]. It must also slow down all the reaction channels leading to formation of the elements hydrogen and soot, where “soot” is used here for elemental carbon of ill-defined structure.

Catalysts for C–H activation of unfunctionalized hydrocarbons must have the following profile:

1. activate only C–H and not C–C
2. bind alkane molecules specifically at one site
3. not bind olefins or aromatic compounds strongly
4. operate in site isolation, prevent the formation of adjacent activated molecules (polycondensation to carbon)

It is possible with this profile to derive a few rules of thumb for choosing suitable catalysts. It is clear that late transition metals in the form of large crystals are not suitable, despite their very strong C–H activating function. All group 8 elements are strong activators and lead to rapid and deep dehydrogenation. An active and selective system can be generated if the particle size of the metal is reduced such that only one activating site per particle is left and if, as consequence of this nano-size, the electronic structure is suitably modulated to reduce the activating effect of a high density of electronic states near the Fermi level [18–20]. The use of highly disperse platinum on alumina [21–24] is a practical outcome of this consideration.

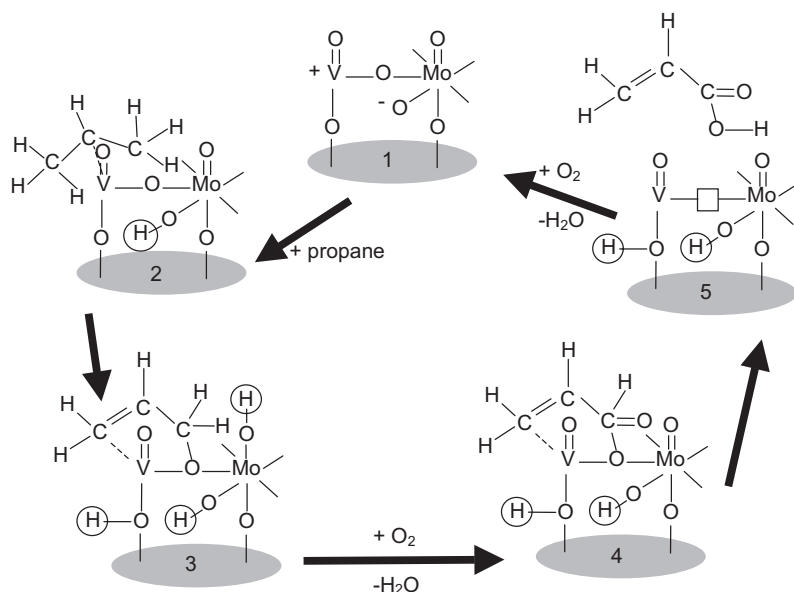
The other option is to use transition metal oxides in high formal oxidation states as strong Lewis acids activating C–H groups without reacting with the carbon skeleton. Oxides of Cr, V, Ni, Fe, Ti, Mo, and Nb, in order of decreasing efficiency, are candidates [25–39]. It is, however, inappropriate to use stable bulk phases of such oxides. They are terminated at their surface with stable oxygen functionality and do not expose the required undercoordinated sites. In addition, these oxides contain some covalent bonding which reduces the Lewis acidity of a given site in dense stable structures [40]. For these reasons it is essential to bind the active site into a matrix of oxidizing nature that stabilizes the high oxidation

state, supports the chemical transformation by holding the reagents, and site-isolates the active center(s) as a result of reduced electronic interaction between active site and matrix. Such conditions are fulfilled best in loosely packed complex structures [41] that are generated as “defects” from dense parent structures of multi-element oxides [42, 43], or in active oxide nanoparticles supported on strongly binding oxides [44].

Scheme 2 illustrates such a configuration, with a simplified reaction sequence for the C–H transformation of propane. Step (1) shows a mixed-metal cluster consisting of a tetrahedrally coordinated vanadium site and an octahedrally coordinated molybdenum center residing firmly on its matrix. This stabilization is of key importance, because many chemical bonds in the cluster are modified in the reaction sequence and without a fixation it will fall apart. On the other hand, this binding must be local to preserve the electronic structure of the defective situation indicated by the formal charges. In step (2) activation of propane to an allylic cationic species occurs as a result of the abstraction of one hydrogen atom. This step is facile and was shown to occur at 300 K in model reactions using VO_2^+ cations colliding in an ion-cyclotron-resonance Fourier-transform mass spectroscopic experiment with propane. Consecutive C–H transfers to oxygen sites at the reactive cluster lead to species (3) which is a stable propenyl complex for which evidence was also found in the above mentioned mass spectroscopic model experiments. Hydrogenolysis of the alkoxy bond can occur at sufficiently high temperatures and propene is released. At even higher temperatures the two remaining OH groups dehydrogenate to hydrogen and the defective cluster. This scenario is not likely to occur because the remaining oxygen species in the cluster are activated or gas phase oxygen reacts with the reduced metal sites at elevated reaction temperatures. Consecutive steps are the hetero-functionalization with oxygen to acrolein (step 4) and acrylic acid (step 5). Regeneration of the active cluster occurs by activation of a second oxygen molecule at the vacancy or addition of two lattice oxygen species from the matrix.

The complexity of designing such catalysts arises because the C–H transformation function wanted is not the property of a bulk solid or a well-defined surface but of defects in phases. Such catalysts resemble their biological counterparts, the enzymes that consist also of a complex matrix holding the active site in place and in suitable electronic isolation. The ability to mimic this principle in heterogeneous catalysis with the concept of “single site” catalysts [45–47] has led to first academic success but is still far away from practical realization, because of the lack of suitable procedures for synthesis of bulk quantities of highly active material.

The essential characteristics of the active species of such catalysts are the co-existence of metal centers in different co-ordination to minimize the energy required for defect formation. It is not necessary that two transition metals are combined, but the arrangement shown in Scheme 2 seems to be of high stability, because it occurs in many technical catalysts for C_2 and C_3 oxo-functionalization [48–51]. The structure must also enable the formation of suitably free space around an active site that is yet firmly attached to its support. Homonuclear sup-



Scheme 2. Critical reaction steps during C–H activation and consecutive selective oxidation. The gray surface represents the matrix of an active site of a metal oxide catalyst. The first product desorbing from such a catalyst

would be propene in step 3. Hydrogenolysis of the alkoxy interaction between substrate and catalyst controls the branching ratio between the consecutive selective oxidation and the desorption of the olefin.

ports (i.e. oxides of composition similar to active clusters such as $[\text{Mo}_x\text{V}_y\text{O}_{14}]$) are good choices, rendering the detection of such self-supported structures difficult. The anchoring to the support is also delicate, because it should provide stable connections and even polarize the cluster so as to facilitate defect formation but it may not redistribute local charges at the cluster sites through extensive covalent interactions. This specific bonding at a defect site is considered as the atomistic analog of the long-proposed site-isolation [52] that has its foundation in a kinetic argument. The electronic structure of an active site is locally different from that of the matrix and it should not enable equilibration of charge imbalances through the bulk solid.

Given the complexity of the reaction possibilities and the little structural knowledge we still have about such systems, it may be asked where the specificity of the reaction pathway comes from and what makes the reaction stop at the level of two oxygen additions instead of continuing all the way to deep oxidation that is thermodynamically so favorable. Model experiments with isolated clusters combined with high-level theoretical analysis and reactivity studies of surface-science grade well-defined oxide surfaces lead to several conclusions.

1. The specificity of an oxide catalyst depends on its local electronic structure, both the electron density and the spin density. Making and breaking of bonds affects the spin of the active metal – spin-allowed reactions are kinetically faster and thus have an advantage over spin-forbidden reactions.

Thus, the change in oxidation state that would alter the spin is either essential to cater for spin-forbidden transitions or should not occur, to let a spin-allowed reaction to occur rapidly. This principle of specificity was identified in a large array of metal-oxo cluster reactions with small molecules [53, 54] and should be transferable to real catalyst under the concept of local electronic structures at active sites.

2. A given catalyst reacts with different small alkanes according to different reaction pathways. It is not correct to assume a gross similarity between different small alkane molecules [55]. The reason is that according to topology of the reactant-cluster geometry different reaction pathways open up with increasing complexity from C_2 via C_3 to C_4 molecules.
3. Defects are, indeed, essential for reactivity of oxide surfaces. When single-crystalline oxides are prepared free from oxygen vacancies [56, 57] surface terminations are observed to be very stable and chemically inert. Only if defects are produced in such surfaces by drastic reduction with hydrogen or ion bombardment is chemical reactivity observed; this reactivity seems to be closely related to the loss in long-range surface ordering. It has also been found that metal–oxygen double bonds occur in many systems [58] irrespective of the existence of such bonds in stable molecular species.
4. These metal–oxygen double bonds seem to guarantee the preservation of the structure of a reacting cluster but they may not cover the entire surface. In gas phase model experiments [55] it has been shown that one $V=O$ bond prevails during all reaction steps whereas the other vanadium–oxygen interaction in the VO_2^+ system studied changed its bond order, thus enabling it to act as an acceptor for carbon or hydrogen. Metal–oxygen double bonds, coordination defects exposing the metal cation to the substrate, and metal–oxygen bridges providing chemical reactivity are required to co-exist in an active site for C–H transformation of an alkane molecule. This explains the difficulty of “designing” such an active site, which is far more complex than a single metal ion in a high formal oxidation state.

In summary, catalytic C–H transformations in small unfunctionalized alkanes is a technically very important family of reactions and processes leading to small olefins or to aromatic compounds. The prototypical catalysts are chromia on alumina or vanadium oxides on basic oxide supports and platinum on alumina. Reaction conditions are harsh with a typical minimum temperature of 673 K at atmospheric pressure and often the presence of excess steam. A consistent view of the reaction pathway in the literature is the assumption that the first C–H abstraction should be the most difficult reaction step. It is noted that other than intuitive plausibility there is little direct evidence in heterogeneous reactions that this assumption is correct. From the fact that many of these reactions are highly selective toward aromatic compounds or olefins it must be concluded that later events in the sequence of elementary steps are possibly more likely candidates for the rate-determining step that controls the overall selectivity. A detailed description of the individual reactions of C_2 – C_4 alkanes can be found in a comprehensive review [59].

2.6

Transition-metal Catalyzed Carboxylation of Alkanes

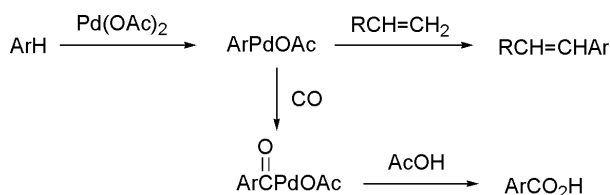
Yuzo Fujiwara and Tsugio Kitamura

2.6.1

Introduction and Fundamental Examples

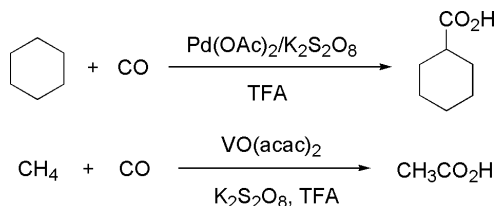
Alkanes are abundantly and cheaply available from petroleum oil and natural gas. Their utilization is, therefore, of great practical interest and the activation and functionalization of C–H bonds of alkanes is an important, promising route for future synthesis of functional materials. It is, however, difficult to achieve the functionalization of alkanes because they are unreactive, owing to the low reactivity of alkane C–H bonds.

During the development of palladium-catalyzed coupling reaction of arenes with alkenes, we found that σ -arylpalladium complexes reacted with CO to give aromatic acids in AcOH, as shown in Scheme 1 [1]. This carboxylation reaction of arenes with CO proceeds catalytically with regard to Pd at room temperature under atmospheric pressure of CO, when $K_2S_2O_8$ is added as oxidant and trifluoroacetic acid (TFA) is used as the solvent.



Scheme 1. Pd-catalyzed reactions of arenes with alkenes or CO.

Alkanes also undergo carboxylation with CO, as shown in Scheme 2. Carboxylation of alkanes to carboxylic acids is one of the interesting and important functionalization processes. The first example of carboxylation of alkanes was performed on cyclohexane using a $\text{Pd(OAc)}_2/K_2S_2O_8/\text{TFA}$ catalyst system [2]. This carboxylation reaction was extended to gaseous alkanes, for example methane, ethane, and propane. Thus, acetic acid (AcOH) was synthesized from methane and CO in the presence of a Pd catalyst but with a low conversion yield [3]. Recently, the acetic acid synthesis was much improved by using vanadium catalysts such as VO(acac)_2 and afforded AcOH almost quantitatively [4].

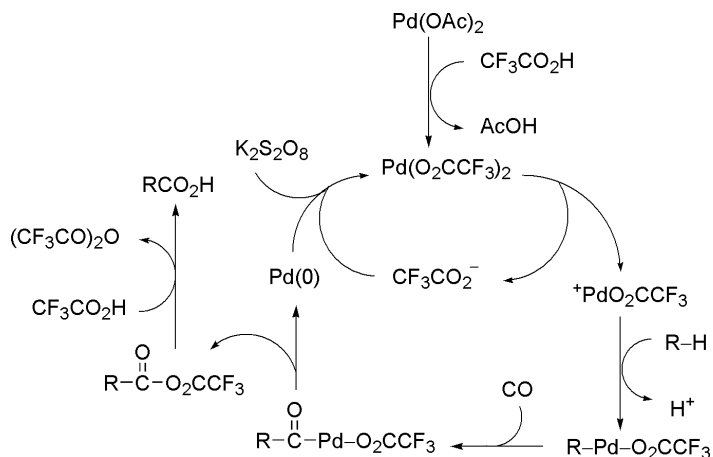


Scheme 2. Representative carboxylation reactions of alkanes.

2.6.2

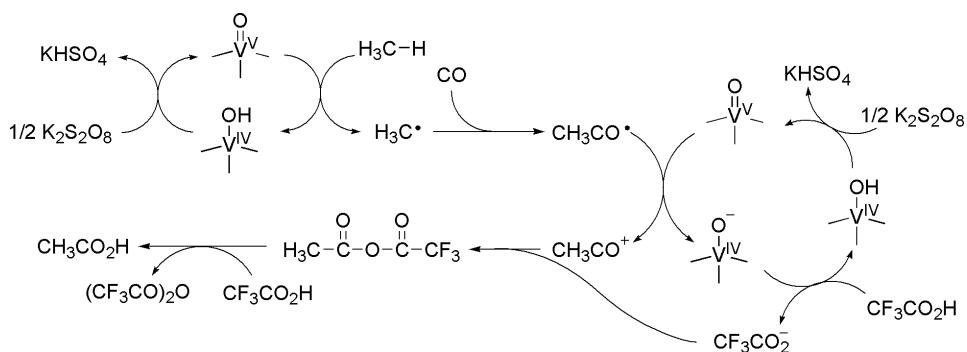
Mechanism

As illustrated in Scheme 3 [1a], palladium-catalyzed carboxylation of alkanes may proceed in a fashion similar to the carboxylation of arenes, involving electrophilic attack of cationic $[\text{PdO}_2\text{CCF}_3]^+$ species on the C–H bonds of alkanes to give alkyl– $\text{Pd}(\text{II})\text{--O}_2\text{CCF}_3$ species.



Scheme 3. Electrophilic carboxylation by Pd

For the vanadium-catalyzed reaction, the involvement of radical species has been suggested [4], as shown in Scheme 4. The oxovanadium(V) species could abstract an H atom from CH_4 to form the methyl radical CH_3^\bullet , which could react with CO to give the acetyl radical $\text{CH}_3\text{CO}^\bullet$. Oxidation of $\text{CH}_3\text{CO}^\bullet$ to CH_3CO^+ by $\text{V}(\text{V})=\text{O}$ would give acetic acid.



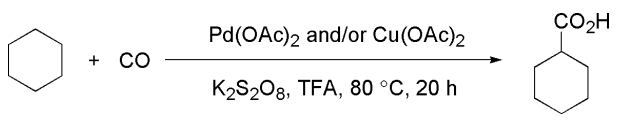
Scheme 4. A possible mechanism for formation of acetic acid from methane and CO.

2.6.3

Scope and Limitations

Cyclohexane has been carboxylated with CO by using a $\text{Pd}(\text{OAc})_2$ catalyst in the presence of $\text{K}_2\text{S}_2\text{O}_8$ as oxidant in TFA at 80°C [2]. Addition of $\text{Cu}(\text{OAc})_2$ among metal additives such as Fe, FeCl_2 , $\text{Co}(\text{OAc})_2$, $\text{Ni}(\text{OAc})_2$, $\text{Cu}(\text{OAc})_2$, and $\text{Zn}(\text{OAc})_2$, had a drastic effect on the formation of cyclohexanecarboxylic acid. The role of three metal salts; $\text{Pd}(\text{OAc})_2$, $\text{Cu}(\text{OAc})_2$, and $\text{K}_2\text{S}_2\text{O}_8$, is summarized in Table 1. The best result was obtained in the reaction using $\text{Pd}(\text{OAc})_2$ (0.1 mmol), $\text{Cu}(\text{OAc})_2$ (0.2 mmol), and $\text{K}_2\text{S}_2\text{O}_8$ (9 mmol), giving 1981 % yield of cyclohexanecarboxylic acid based on $\text{Pd}(\text{OAc})_2$ (4.3 % yield based on cyclohexane).

Table 1. Carboxylation of cyclohexane with CO.^a

			
$\text{Pd}(\text{OAc})_2$ (mmol)	$\text{Cu}(\text{OAc})_2$ (mmol)	$\text{K}_2\text{S}_2\text{O}_8$ (mmol)	Yield (%) ^b
0.1	–	–	Trace
–	0.2	–	0
–	–	9	1.7 (0.3)
0.1	0.2	–	Trace
0.1	–	9	260 (0.6)
–	0.2	9	148 (0.6)
0.1	0.2	9	1981 (4.3)

^a Cyclohexane (5 mL), TFA (3.3 mL), CO (20 atm)

^b Based on the limiting metal salt. Values in parentheses are based on cyclohexane.

Gaseous alkanes such as methane, ethane, and propane were also carboxylated to give acetic, propionic, and butyric acids, respectively, as shown in Table 2 [2a, 3b]. Ethane and propane were best carboxylated by the mixed catalyst of $\text{Pd}(\text{OAc})_2$ and $\text{Cu}(\text{OAc})_2$, whereas reaction of methane was not effective under the action of the same catalytic system. For methane $\text{Cu}(\text{OAc})_2$ gave the best result among the catalysts employed, as shown in Table 2. However, the yield of acetic acid based on methane is low.

Table 2. Carboxylation of methane, ethane, and propane with CO.^a

$$\text{C}_n\text{H}_{2n+2} + \text{CO} \xrightarrow[\text{K}_2\text{S}_2\text{O}_8, \text{TFA}, 80^\circ\text{C}, 20\text{ h}]{\text{Pd}(\text{OAc})_2 \text{ and/or } \text{Cu}(\text{OAc})_2} \text{C}_n\text{H}_{2n+1}\text{CO}_2\text{H}$$

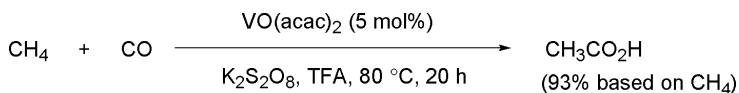
Alkane	Carboxylic acid	catalyst and yield (%) ^b		
		Pd(OAc) ₂ -Cu(OAc) ₂	Pd(OAc) ₂	Cu(OAc) ₂
Propane	Butyric acid ^c	7100 (8.7)	1760 (2.1)	1900 (2.2)
Ethane	Propionic acid	7600 (2.1)	440 (0.2)	700 (0.3)
Methane	Acetic acid	1300 (0.4)	100 (0.03)	2960 (0.9)

^a Propane (10 atm), ethane (30 atm), methane (40 atm), Pd(OAc)₂ (0.05 mmol), Cu(OAc)₂ (0.05 mmol), K₂S₂O₈ (10 mmol), TFA (5 mL), and CO (20 atm)

^b Based on the catalyst. Values in parentheses are based on alkanes

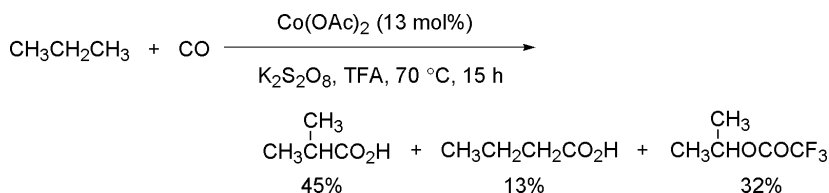
^c A mixture of isobutyric and butyric acids (4:1)

We recently found that vanadium-catalysts were very active in carboxylation of alkanes, and the VO(acac)₂ catalyst in the presence of K₂S₂O₈ and TFA afforded acetic acid almost quantitatively from methane and CO [4]. The reaction of methane (5 atm) with CO (20 atm) at 80 °C for 20 h gave acetic acid in 93 % yield based on methane, as shown in Scheme 5. Other vanadium compounds, for example V₂O₃, V₂O₅, and NaVO₃ and a variety of vanadium-containing heteropolyacids (H₅PV₂Mo₁₀O₄₀, H₄PVW₁₁O₄₀, and H₅SiVW₁₁O₄₀) were also highly active as catalysts.

**Scheme 5.** Carboxylation of methane by VO(acac)₂, VO(acac)₂ (0.05 mmol), CH₄ (5 atm), CO (20 atm), K₂S₂O₈ (10 mmol), TFA (20 mL), 80 °C, 20 h.

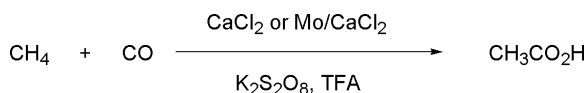
Interestingly, Co(OAc)₂ has been found to be an efficient catalyst for carboxylation of propane [5]. For example, reaction of propane (1 atm) with CO (30 atm) in the presence of Co(OAc)₂ (0.1 mmol) and K₂S₂O₈ (10 mmol) in TFA gave butyric acids in 58 % yield, based on propane.

Surprisingly, CaCl₂ was also found to be effective in the carboxylation of alkanes such as ethane, propane, and cycloalkanes by CO in the presence of K₂S₂O₈ and TFA [6, 7]. With methane acetic acid was formed almost quantitatively by using CaCl₂ as catalyst, although a long reaction time (140 h) was required [7]. In TFA, methane and CO could be converted to acetic acid by the catalytic system



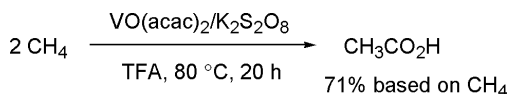
Scheme 6. Carboxylation of propane by Co(OAc)_2 ; Co(OAc)_2 (0.1 mmol), propane (1 atm), CO (30 atm), $\text{K}_2\text{S}_2\text{O}_8$ (10 mmol), TFA (5 mL), 70°C , 15 h.

$\text{Mo/CaCl}_2/\text{K}_2\text{S}_2\text{O}_8/\text{TFA}$ [8]. The best result (89.4 % acetic acid) was obtained in the reaction of methane (20 atm) and CO (50 atm) using the catalytic system at 85°C for 20 h.



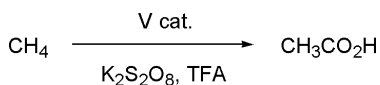
Scheme 7. (a) CaCl_2 (0.5 mmol), methane (2 atm), CO (30 atm), $\text{K}_2\text{S}_2\text{O}_8$ (5 mmol), TFA (5 mL), TFAA (2 mmol), 85°C , 140 h; (b) Mo powder (0.2 mmol), CaCl_2 (0.4 mmol), $\text{K}_2\text{S}_2\text{O}_8$ (5 mmol), TFA (10 mL), 85°C , 20 h.

Interestingly, it was found that reaction of methane, without CO, in the presence of VO(acac)_2 , $\text{K}_2\text{S}_2\text{O}_8$, and TFA gave acetic acid [9]. Reaction of $^{13}\text{CH}_4$ afforded $^{13}\text{CH}_3^{13}\text{CO}_2\text{H}$. This result suggests that the carbon source of acetic acid is methane.



Scheme 8. Acetic acid formation from methane. Methane (5 atm), VO(acac)_2 (0.05 mmol), $\text{K}_2\text{S}_2\text{O}_8$ (5 mmol), TFA (20 mL), 80°C , 20 h.

The oxovanadium(V) complex $\text{VO(N(CH}_2\text{CH}_2\text{O)}_3)$ and Amavadinine $\text{Ca[V(ON(CH(CH}_3\text{)COO)}_2)_2]$ are also very active in the conversion of methane into acetic acid in the absence of CO [10], as shown in Table 3. Although the detailed mechanism is not clear, the isotope experiment using $^{13}\text{CH}_4$ suggests that CH_4 is the source of the methyl group of acetic acid and the carbon source of the carboxylic acid group is TFA.

Table 3. Carboxylation of methane in the presence or absence of CO.^a

Catalyst ^b	Methane (atm)	CO (atm)	Time (h)	TON ^c	Yield (%) ^d
1	5	–	20	10.0	21.4
1	5	5	20	10.9	23.5
1	12	15	20	28.2	25.6
2	5	–	20	13.4	29.4
2	5	15	20	12.0	54.3

^a Metal complex catalyst (0.0625 mmol), K₂S₂O₈ (12.5 mmol), TFA (23 mL), 80 °C

^b 1: VO(N(CH₂CH₂O)₃), 2: Ca[V(ON(CH(CH₃)COO)₂)₂]

^c Turnover number

^d Based on methane

Experimental

Cyclohexanecarboxylic acid

A 50-mL centrifuge glass tube equipped with a Teflon-coated magnetic stirring bar was charged with Pd(OAc)₂ (0.02 mmol), Cu(OAc)₂ (0.02 mmol), and TFA (2.3 mL). The solution was stirred for 5 min. Cyclohexane (5 mL) and K₂S₂O₈ (9.0 mmol) were then added to the solution. A rubber septum with a glass needle was fitted to the tube, which was placed in a 100-mL stainless-steel autoclave. The autoclave was closed and pressurized to 20 atm with CO. The mixture was heated at 80 °C for 20 h with stirring. After cooling and venting of the residual gas, the autoclave was opened and the mixture was filtered. The precipitates were washed with benzene. The filtrate was diluted with 2 M HCl solution, extracted with benzene, and washed with brine. The aqueous layer was further extracted with chloroform. The combined organic layer was dried over anhydrous MgSO₄ and concentrated in vacuo. The product was analyzed by GLC.

Acetic Acid

VO(acac)₂ (0.05 mmol), K₂S₂O₈ (10 mmol), TFA (10 mL), and a Teflon-coated magnetic stirring bar were placed in a 25-mL stainless-steel autoclave. The autoclave was closed, flushed three times with CO, and pressurized to 20 atm with CO (3.80 mmol) and then to 5 atm with CH₄ (0.94 mmol). The mixture was heated at 80 °C, with stirring, for 20 h. After cooling and venting of residual gases the autoclave was opened and the mixture was analyzed directly by GLC to give acetic acid (0.87 mmol) in 93 % yield based on methane.

2.7

Photochemical and Thermal Borylation of Alkanes

John F. Hartwig and Joshua D Lawrence

2.7.1

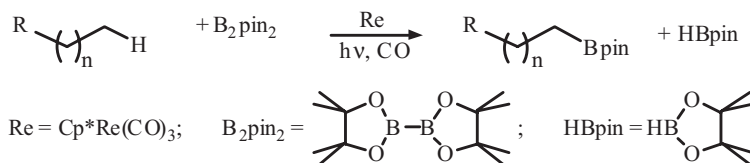
Introduction and Fundamental Examples

Most current regioselective, catalytic functionalization of saturated C–H bonds [1–5] occurs by directed processes [6–13]. In these processes the catalyst or reagent docks at a functional group or reacts at C–H bonds that are located α to a heteroatom, because these bonds are weaker than more distal ones [14]. Borylation of methyl C–H bonds complements the directed chemistry because it occurs at unactivated C–H bonds with regioselectivity that is independent of the position of the functional group in the reagent [15].

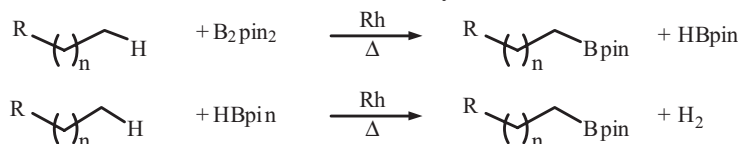
2.7.1.1 Borylation of Alkanes

Borylation is the photochemically or thermally promoted conversion of substrates with C–H bonds into boronate esters using bis(pinacol)diborane(4) (B_2pin_2) or pinacolborane (HBpin) reagents (Scheme 1) [16–35]. The selectivity for methyl C–H bonds and the versatility of organoboron reagents [36, 37] give alkane borylation potential for use in synthetic contexts.

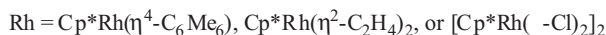
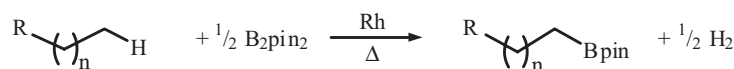
Photochemical Alkane Borylation



Thermal Alkane Borylation



Netreaction:



Scheme 1. Borylation of alkanes by B_2pin_2 and HBpin reagents.

2.7.1.2 Thermodynamics of Alkane and Arene Borylation

The bond dissociation energies (BDE) of both bonds formed in the reaction of B_2pin_2 with alkanes are larger than those of both bonds broken by 10–20 kcal mol^{−1}. Borylation of alkanes with HBpin is less exergonic. The reaction of HBpin with alkanes is unusual. The dehydrogenative coupling of alkanes with most HX compounds, in which X is an electronegative element or electronegative group, is endergonic, because the H–X bond is much stronger than the C–X bond. In contrast with the different energies of the H–X and C–X bonds of reagents with electronegative atoms or groups, X, the energies of H–B and C–B bonds of boranes are similar. The C–B bond is even slightly stronger than the H–B bond [38]. The sum of the BDE of the C–B (112 kcal mol^{−1}) and H–H (104 kcal mol^{−1}) bonds formed during the borylation of methane by HBpin is approximately the same as the sum of the BDE of the C–H (105 kcal mol^{−1}) and B–H (111 kcal mol^{−1}) bonds broken.

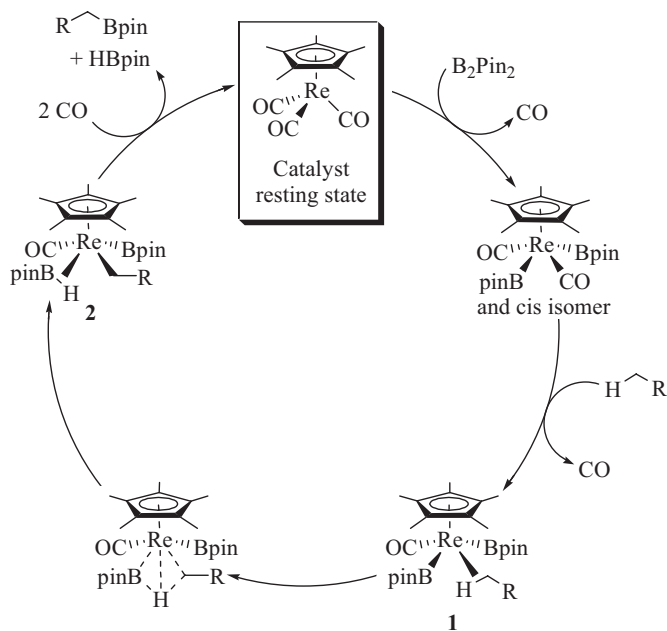
2.7.2

Mechanism

Stoichiometric borylation of alkanes by isolated $Cp^*M(CO)_x(BR_2)_y$ complexes [26, 29, 39, 40] led to the discovery of complexes that catalyze the borylation of arenes and alkanes [18, 33, 41]. The key step in the mechanism of the borylation of hydrocarbons involves the reaction of transition metal–boryl complexes [19, 25, 32, 42, 43] with C–H bonds to form boronic esters and metal-hydrides. Catalytic systems regenerate the metal boryl complex from the metal hydride product by elimination of H₂ or borane upon reaction of the metal hydride with borane or diborane(4) reagent, respectively. Borylation of hydrocarbons has been catalyzed by Re [41], Rh [18, 24, 25, 44, 45], Pd [46], and Ir [18, 19, 22, 23, 32, 42, 45, 47], complexes. In addition, the stoichiometric borylation of hydrocarbons has been demonstrated with Mn [29, 39], Fe [29, 39], Mo [21, 26], Ru [21, 26], W [21, 26], and Re [21, 29, 39] complexes.

2.7.2.1 Photochemical Borylation of C–H bonds

The photochemical borylation of alkanes (Scheme 1) occurs as a result of photochemical dissociation of a carbonyl ligand from the catalyst precursor, $Cp^*Re(CO)_3$ (Scheme 2) [41]. After this dissociation of CO, oxidative addition of B_2pin_2 forms *cis*- and *trans*- $Cp^*Re(Bpin)_2(CO)_2$. These complexes have been isolated from the stoichiometric, photochemical reaction of $Cp^*Re(CO)_3$ with B_2pin_2 . On photolysis this mixture of isomers reacts with pentane to form the pentylboronate ester in quantitative yield. This finding strongly suggests that the bisboryl complexes lie on the catalytic cycle. Alkane activation most probably occurs by dissociation of a carbonyl ligand, coordination of a C–H bond to form a σ -complex (1), and σ -bond metathesis [21] to generate a σ -borane complex (2). Reductive elimination of the alkylboronate ester, dissociation of HBpin, and coordination of two carbonyl ligands would complete the catalytic cycle.

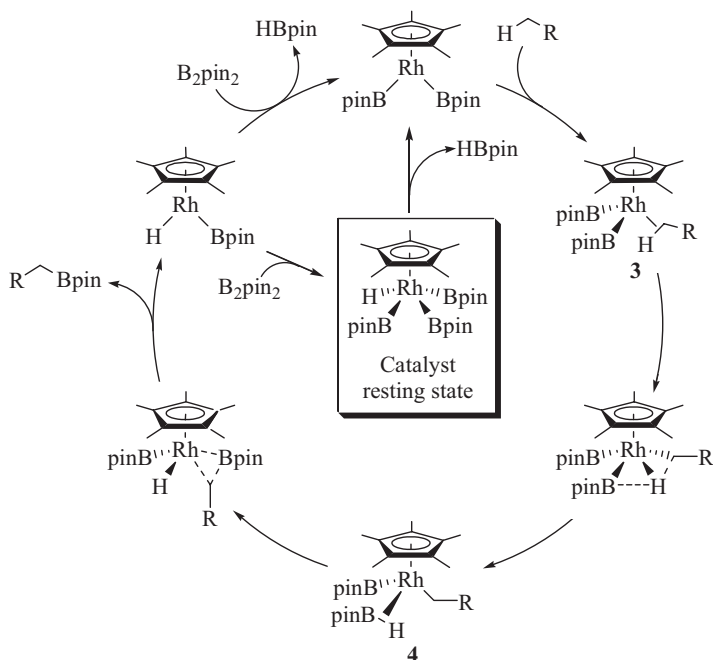


Scheme 2. Proposed mechanism of photochemical C–H borylation catalyzed by $\text{Cp}^*\text{Re}(\text{CO})_3$.

2.7.2.2 Thermal Borylation of C–H bonds

The mechanism of thermal borylation of alkanes seems to be similar to that of photochemical borylation of alkanes. The most active precatalysts for thermal alkane borylation, $\text{Cp}^*\text{Rh}(\eta^4\text{-C}_6\text{Me}_6)$ and $\text{Cp}^*\text{Rh}(\eta^2\text{-C}_2\text{H}_4)$, are converted to mixtures of $\text{Cp}^*\text{Rh}(\text{Bpin})_3(\text{H})$ and $\text{Cp}^*\text{Rh}(\text{Bpin})_2(\text{H})_2$ in the catalytic reactions [48]. Reaction of HBpin or B_2pin_2 with $\text{Cp}^*\text{Rh}(\text{Bpin})_2(\text{H})_2$ yields $\text{Cp}^*\text{Rh}(\text{Bpin})_3(\text{H})$. Furthermore, reaction of $\text{Cp}^*\text{Rh}(\text{Bpin})_3(\text{H})$ with alkanes and arenes as solvent yields $\text{Cp}^*\text{Rh}(\text{Bpin})_2(\text{H})_2$. Both species are kinetically capable of being catalysts of the borylation of alkanes.

Computational studies performed on model complexes in collaboration with Hall and coworkers suggest that alkane borylation may occur by a σ -bond metathesis pathway (Scheme 3) [48]. The proposed mechanism for the borylation of alkanes by **1** begins with elimination of HBpin to generate the 16-electron complex $\text{Cp}^*\text{Rh}(\text{Bpin})_2$. This complex then forms a σ -complex (**3**) with the alkane. The vacant p-orbital on boron then enables σ -bond metathesis to generate a σ -borane complex (**4**). Reductive elimination of the alkylboronate ester product and oxidative addition of B_2pin_2 then regenerate **1**.



Scheme 3. Mechanism of C–H borylation catalyzed by $\text{Cp}^*\text{Rh}(\text{H})(\text{Bpin})_3$.

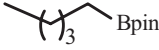
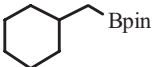
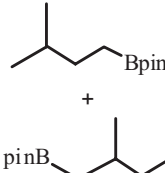
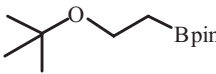
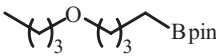
2.7.3

Scope and Limitations

2.7.3.1 Photochemical Borylation of Methyl C–H Bonds

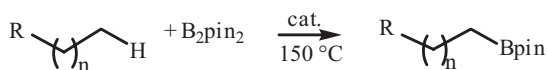
Both $\text{Cp}^*\text{Re}(\text{CO})_3$ and $\text{Cp}^*\text{Re}(\text{Bpin})_2(\text{CO})_2$ catalyze the photochemical borylation of alkanes and alkyl ethers (Table 1). The yield of the photochemical borylation of alkanes depends on the steric hindrance around the methyl groups. For example, the borylation of pentane proceeds with higher yields than the borylation of methylcyclohexane (Table 1, entries 1 and 2), and the functionalization of the less hindered 4-position of isopentane occurs more than three times faster than the borylation of the more hindered 1-position (Table 1, entry 3). The greater yield for borylation of *n*-butyl ether compared with *tert*-butyl ethyl ether (Table 1, entries 4 and 5) also indicates that the efficiency of borylation depends on the steric accessibility of the methyl groups. The borylation of alkanes with HBpin as reagent, which occurs under thermal conditions, was not observed under photochemical conditions.

Table 1. Substrate scope of Re-catalyzed photochemical alkane borylation.
$$\text{R}-(\text{CH}_2)_n\text{H} + \text{B}_2\text{pin}_2 \xrightarrow[\text{hv, CO (2atm)}]{\text{Cp}^*\text{Re}(\text{CO})_3} \text{R}-(\text{CH}_2)_n\text{Bpin} + \text{HBpin}$$

Product	Catalysts, mol%	Time (h)	Yield (%)	Entry
	Cp*Re(CO) ₃ , 2.4	56	95	1
	Cp*Re(CO) ₃ , 5.0	60	75	2
	Cp*Re(CO) ₃ , 3.4	55	65 + 18	3
	Cp*Re(CO) ₃ , 5.0	45	100	4
	Cp*Re(CO) ₃ , 4.9	46	82	5

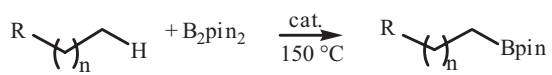
2.7.3.2 Thermal Borylation of Methyl C–H Bonds

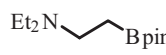
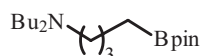
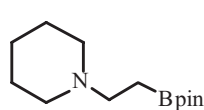
The borylation of alkanes under thermal conditions is catalyzed by Cp*Rh(C₂H₄)₂, Cp*Rh(C₆Me₆), and (Cp*RhCl₂)₂. Reactions initiated with Cp*Rh(C₆Me₆) as precatalyst usually give the highest yield of borylation products (Table 2, entries 6–9). Rhodium-catalyzed borylation of methyl C–H bonds in protected alcohols, protected ketones, fluoroalkanes, and amines proceeds in good yield and with the same selectivity for methyl groups observed during the reactions of alkanes (Table 2) [18, 41, 49]. Little or no reaction between HBpin and the acetal, *tert*-butyl ether, and fluoroalkanes is observed. No product is observed from functionalization α to the electron-withdrawing substituents, even though these C–H bonds are weaker than methyl C–H bonds [14, 38, 50–54]. This is the first example of regiospecific C–H functionalization at unactivated sp³ hybridized C–H bonds in presence of functional groups that could direct or inhibit C–H activation.

Table 2. Substrate scope of Rh-catalyzed thermal alkane borylation.

Product	Catalyst, mol%	Time (h)	Yield (%)	Entry
	Cp*Rh(C ₂ H ₄) ₂ , 5	5	84 ^a	6
	Cp*Rh(C ₂ H ₄) ₂ , 1	110	64 ^a	7
	Cp*Rh(C ₆ Me ₆), 5	25	88 ^a	8
	Cp*Rh(C ₆ Me ₆), 1	80	72 ^a	9
	Cp*Rh(C ₆ Me ₆), 6	80	49 ^a	10
	Cp*Rh(C ₂ H ₄) ₂ , 2.5	30	61 ^a	11
			+ 12 ^a	
	Cp*Rh(C ₆ Me ₆), 4	80	64 ^b	12
	Cp*Rh(C ₆ Me ₆), 5	24	91 ^b	13
	Cp*Rh(C ₆ Me ₆), 5	24	74 ^b	14
	Cp*Rh(C ₆ Me ₆), 5	24	83 ^b	15
	Cp*Rh(C ₆ Me ₆), 5	24	90 ^b	16

Table 2. Continued



Product	Catalyst, mol%	Time (h)	Yield (%)	Entry
	Cp*Rh(C ₆ Me ₆), 5	24	69 ^a	17
	Cp*Rh(C ₆ Me ₆), 5	24	75 ^a	18
	Cp*Rh(C ₆ Me ₆), 5	24	55 ^a	19

^a Yield based on conversion to H₂^b Yield based on conversion to HBpin

2.7.3.3 Selectivity Between Methyl C–H Bonds

Yields in the thermal borylation of alkanes depend on the concentration of methyl groups, and on steric hindrance about the methyl group. For example, the borylation of octane occurs gives nearly twice the yield of borylation of methylcyclohexane (Table 2, entries 6 and 10). The borylation of isopentane occurs preferentially at the least hindered methyl group with a selectivity that is slightly higher than that observed in the photochemical reaction. Furthermore, no product from the borylation of methyl C–H bonds of the *tert*-butyl group of *tert*-butyl ethers or the methyl C–H bonds of a pinacol group is observed. Reactions of substrates with equivalent methyl groups, for example tributylamine, generate a mixture of mono- and difunctionalized products when the organic substrate is the limiting reagent.

As shown in Scheme 4, borylation occurs preferentially at the sterically accessible methyl group closest to the heteroatom, and the effect of the more electronegative oxygen in the ether is larger than that of the more coordinating and basic nitrogen in the amine. The same selectivity is observed from an intermolecular competition between ethyl butyl ether and dibutyl ether, after correcting for the ratio of alkyl groups. Consistent with preferential reaction at the less electron-rich methyl group, reaction of a mixture of (perfluoro-*n*-octyl)ethane and octane forms a 94:6 ratio of products that favors borylation of the fluoroalkane [49].

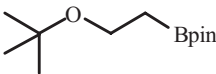
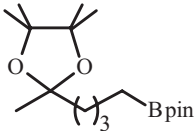

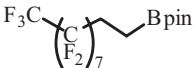
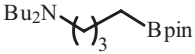
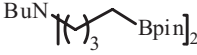
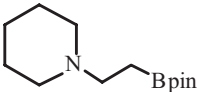


Scheme 4. Site selectivity in the borylation of alkanes with remote electronegative atoms.

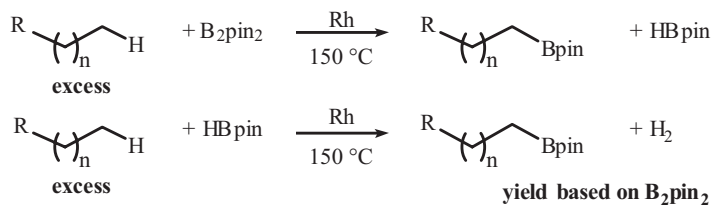
2.7.3.4 Borylation with the Substrate as the Limiting Reagent

Reactions in cyclohexane solvent occur with the reagent and not the cycloalkane, but reactions of compounds with methyl groups without added solvent usually occur in higher yields [49]. The factors that control the yields of the borylation reaction when the substrate is present as the limiting reagent are not well understood. The yield of borylation product of *tert*-butyl ethyl ether is significantly lower than that of the pinacol acetal of 2-hexanone (Table 3, entries 20 and 21) when the two compounds are both the limiting reagents. In contrast, the yields of these products are similar when the ether and acetal are present in excess, relative to the diboron reagent (Table 2, Entries 13 and 14). Yields of the product from the borylation of 1-fluorooctane are markedly different when the substrate is present in excess and as the limiting reagent (Table 2, entry 15; Table 3, entry 22). On the other hand, the yields of the product of borylation of (perfluoro-*n*-octyl)ethane are similar when the substrate is present in excess or as the limiting reagent (Table 2, entry 16; Table 3, entry 23). Although the borylation of tributylamine as limiting reagent is complicated by the formation of mono- and diborylation products (Table 3, entries 24 and 25), the borylation of *N*-ethylpiperidine occurs at the single methyl group in good yield (Table 3, entry 26).

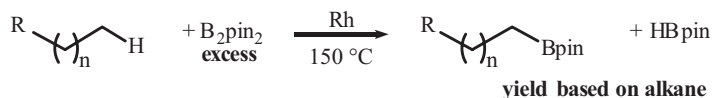
Table 3. Functional group tolerance of alkane borylation under substrate-limiting conditions.
$$\text{R}-(\text{CH}_2)_n\text{H} + \text{B}_2\text{pin}_2 \xrightarrow[150\text{ }^\circ\text{C}]{\text{cat. 1-4 equiv.}} \text{R}-(\text{CH}_2)_n\text{Bpin} + \text{HBpin}$$

Product	Catalyst, mol%	Time (h)	Yield (%)	Entry
	Cp*Rh(C ₆ Me ₆), 10	48	48	20
	Cp*Rh(C ₆ Me ₆), 17	48	70	21
	Cp*Rh(C ₆ Me ₆), 10	48	46	22
	Cp*Rh(C ₆ Me ₆), 10	48	84	23
	Cp*Rh(C ₆ Me ₆), 10	48	33	24
	Cp*Rh(C ₆ Me ₆), 10	48	48	25
	Cp*Rh(C ₆ Me ₆), 10	48	67	26

Borylation in neat substrate

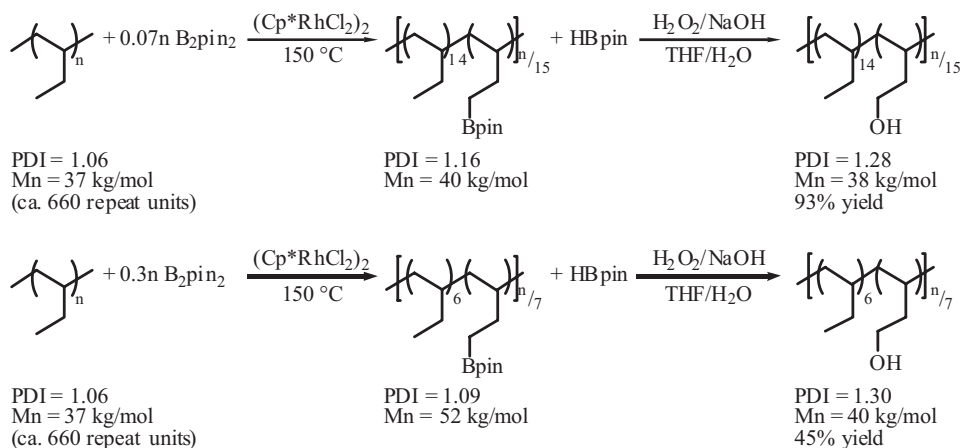


Borylation with the substrate as the limiting reagent

**Scheme 5.** Stoichiometry regimes in alkane borylation.

2.7.3.5 Borylation of Polyolefins

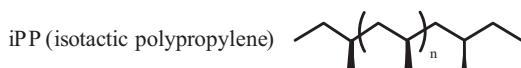
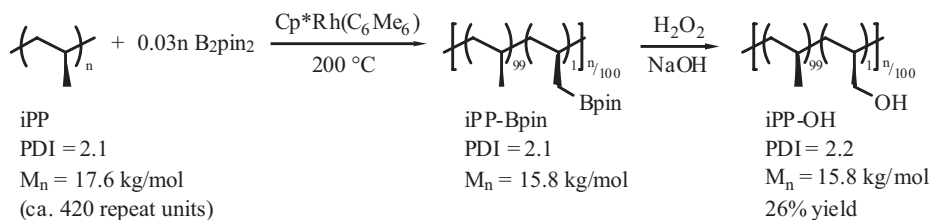
The borylation of alkanes has also been applied to the synthesis of functionalized polyolefins. The borylation of an oligomeric or polymeric polyethylethylene (PEE) occurs exclusively at the primary C–H bonds (Scheme 6). The polymeric alkylboronate esters can be readily converted to the corresponding polymeric primary alcohols by reaction with alkaline solutions of hydrogen peroxide. At a ratio of B_2pin_2 to monomer unit of 7:100, 6.5 of 100 of the methyl groups were converted to hydroxymethyl groups (ca. 1 in 15 or 93 % yield). At a ratio of B_2pin_2 to monomer of 30:100, 14 of the 100 methyl groups were converted to hydroxymethyl groups (ca. 1 in 7 or 45 % yield). In contrast to the functionalization of polyolefins by radical processes, the borylation process does not change the molecular weight distributions (PDI) from those of the starting PEE.



Scheme 6. Functionalization of polyethylethylene.

The regioselective borylation of both model and commercial polypropylenes of varying tacticity has also been accomplished; the functionalization of an isotactic polypropylene, iPP, is shown in Scheme 7 [55]. Rhodium-catalyzed borylation of the polypropylenes, followed by oxidation of the boron-containing material, produced polymers containing 0.2–1.5 % hydroxymethyl side chains. Like the products from the borylation of PEE the products from the borylation of the polypropylenes had the same number-average molecular weights (M_n) and PDI as the starting polypropylenes. Because of the greater steric hindrance of the methyl groups of polypropylene, the efficiencies of the borylation of the polypropylenes were lower than those of the borylation of PEE. Moreover, more crystalline polymers with higher molecular weights underwent functionalization with lower efficiencies. Nevertheless, the rhodium-catalyzed reaction of isotactic polypropylene with an M_n of 17.6 with 3–5 mol% B_2pin_2 per monomer unit led to functionalization of roughly 25 % of the possible number of methyl groups. A hydroxylated isotactic polypropylene was then used as macroinitiator for the aluminum-mediated ring-

opening polymerization of ϵ -caprolactone to prepare polypropylene-graft-polycaprolactone.



Scheme 7. Functionalization of an isotactic polypropylene.

Experimental

2-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptafluoro-decyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

$\text{Cp}^*\text{Rh}(\eta^4\text{-C}_6\text{Me}_6)$ (2.8 mg, 7.0 μmol), B_2pin_2 (35.0 mg, 0.138 mmol), and $\text{CF}_3(\text{CF}_2)_7\text{CH}_2\text{CH}_3$ (61.8 mg, 0.138 mmol) were placed in an NMR tube and sealed under vacuum. The tube was heated at 150 $^\circ\text{C}$ for 24 h. The NMR tube was opened in a drybox, and additional $\text{Cp}^*\text{Rh}(\eta^4\text{-C}_6\text{Me}_6)$ (2.8 mg, 7.0 μmol) and B_2pin_2 (35.0 mg, 0.138 mmol) were added. The tube was again sealed under vacuum and heated for an additional 24 h at 150 $^\circ\text{C}$. Over the course of the reaction, the ^{11}B NMR signal for B_2pin_2 at $\delta = 32 \text{ ppm}$ decreased in intensity, and signals for HBpin and the boronate ester product at $\delta = 27 \text{ ppm}$ and 34 ppm, respectively, increased in intensity. The viscosity of the reaction mixture at room temperature prevented the observation of a well-resolved doublet for HBpin. The NMR tube was opened, and the contents were extracted into benzene. Dodecahydrotriphenylene (16.2 mg, 0.0674 mmol) was added as internal standard, and an aliquot was removed and analyzed by GC. The yield for the reaction of B_2pin_2 to form the functionalized product and HBpin was 84 %. To obtain isolated material for spectral and analytical data, $\text{Cp}^*\text{Rh}(\eta^4\text{-C}_6\text{Me}_6)$ (3.4 mg, 9 μmol), B_2pin_2 (43.7 mg, 0.172 mmol), and $\text{CF}_3(\text{CF}_2)_7\text{CH}_2\text{CH}_3$ (309 mg, 0.688 mmol) were placed into an NMR tube. The tube was sealed under vacuum and heated at 150 $^\circ\text{C}$ for 24 h. After evaporation of the excess (perfluoro-*n*-octyl)ethane, the product was purified by chromatography on silica gel, eluting with pentane, to give 31 mg (31 %) of the boronate ester product. ^1H NMR (C_6D_6 , 500 MHz) $\delta = 2.12 \text{ (m, 2H)}$, 1.00 (t, 2H), 0.99 (s, 12H); ^{11}B NMR (C_6D_6 , 160 MHz) $\delta = 33.7$; ^{13}C $\{^1\text{H}\}$ NMR (C_6D_6 , 126 MHz) $\delta = 120$ to 105 (m, CFs), 83.9, 26.5, 25.1, 4.5, the carbon attached to boron was not observed; ^{19}F NMR (C_6D_6 , 376 MHz) $\delta = -82.1 \text{ (3F, t)}$, -116.8 (2F, m), -122.7 (2F, m), -123.0 (4F, m), -123.9 (2F, m), -124.5 (2F, m), -127.3 (2F, m). Anal. Calcd for $\text{C}_{16}\text{H}_{16}\text{BF}_{17}\text{O}_2$: C, 33.47; H, 2.81. Found: C, 33.65; H, 2.64.

2.8

Preparation of Olefins by Transition Metal-catalyzed Dehydrogenation*Alan S. Goldman and Rajshekhar Ghosh*

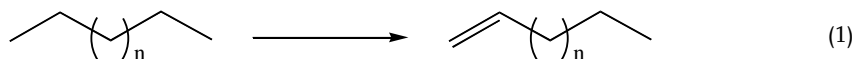
2.8.1

Introduction and Fundamental Examples

Alkanes are the world's most abundant organic resource. Olefins, by contrast, are relatively scarce; they are, however, the most important class of intermediate in the commodity chemical industry [1]. Thus the ability to convert alkanes to alkenes is a reaction with tremendous potential utility. Likewise, in view of the obvious importance of the carbon–carbon double bond functionality in the synthesis of complex organic molecules, the ability to introduce unsaturation into unfunctionalized alkyl groups is also a very alluring goal.

The challenge in alkane dehydrogenation, as in other examples of alkane functionalization (most notably oxidation), is not so much in effecting the reaction but rather accomplishing it in a controlled manner. Thus the oxidation of methane is hardly a challenge (!), but its conversion to methanol is one of the “Holy Grails” of modern chemistry. Likewise, the dehydrogenation of cyclohexane to benzene can be effected by heterogeneous catalysts [2] but the more desirable conversion to cyclohexene in good yield is a long-standing unsolved problem. More generally, the “full” dehydrogenation of small alkanes (ethane, propane, butane to butadiene) can be accomplished reasonably well by high-temperature heterogeneous systems [3] (although in the last cases, C–C cleavage is a significant problem), but the heterogeneously catalyzed conversion of higher alkanes to mono-olefins is not feasible. In general, introduction of a double bond into a higher alkane gives vinylic C–H bonds, which are much weaker than aliphatic bonds and much more reactive toward homolytic and heterolytic cleavage. Furthermore, secondary dehydrogenation to give conjugated double bonds is thermodynamically more favorable than initial dehydrogenation.

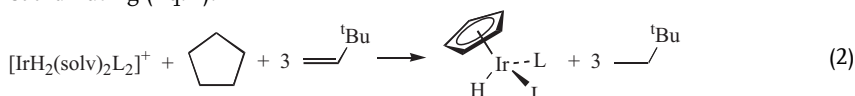
One important specific goal, even more challenging than the mono-unsaturation of alkanes in general, is the dehydrogenation of *n*-alkanes to give α -olefins (Eq. 1).



α -Olefin production currently exceeds 3×10^6 tons year⁻¹ world-wide, mostly by oligomerization of ethylene [4]. *n*-Alkanes are, potentially, a much cheaper feedstock, and one which could afford alpha-olefins with a specific carbon number. The reaction represented by Eq. (1) requires, specifically, activating the strongest C–H bond in an *n*-alkane (primary), to give the thermodynamically least stable double-bond isomer. This goal might therefore seem unfeasible; many transition metal complexes, however, particularly those of the late metals, preferentially undergo addition to the stronger, primary C–H bonds of *n*-alkanes. Although this is only a potential first step, this selectivity in stoichiometric addition has long held promise with respect to functionalization at the terminal position of *n*-alkyl groups.

In addition to examples of stoichiometric reactions with alkanes, late transition-metal complexes also seem promising as dehydrogenation catalysts, in view of the many such complexes that catalyze olefin hydrogenation. Olefin hydrogenation is, however, a highly exothermic reaction ($\Delta H = \text{ca. } -125 \text{ kJ mol}^{-1}$) and so there is a formidable enthalpic barrier to dehydrogenation.

These above-noted points were appreciated by Crabtree, who reported in 1979 that $[(\text{Me}_2\text{CO})_2\text{IrH}_2(\text{PPh}_3)_2]^+$, with use of a hydrogen acceptor, dehydrogenated cyclopentane and cyclooctane (COA) to give the corresponding cycloalkadiene iridium complexes [5]. In mechanistic terms, the presumed role of the acceptor is to generate an active Ir(I) species. *t*-Butylethylene (TBE) was discovered to have the optimum balance of being strongly hydrogen-accepting and weakly coordinating (Eq. 2).



It was proposed that reaction 2 proceeded via C–H “oxidative” addition, although driven largely by the electrophilicity of the cation [6].

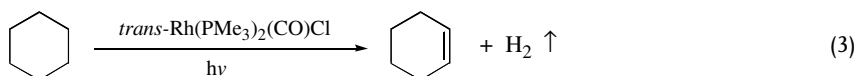
Baudry, Ephritikhine, and Felkin subsequently reported a similar cycloalkane reaction with L_2ReH_7 , also using TBE as hydrogen acceptor, in which the dehydrogenated alkane remained bound to the metal center [7]. This was extended to *n*-pentane, which gave an η^4 -trans-1,3-pentadiene complex. Rather remarkably, attempts to dislodge the coordinated diene with trimethylphosphite gave free 1-alkenes (α -olefins) [8]. Selective conversion of *n*-alkane to 1-alkene was thus achieved, albeit stoichiometrically and via a circuitous route. Cycloalkanes were soon reported to be dehydrogenated catalytically using L_2ReH_7 and L_2IrH_5 [9]. Turnover numbers up to 70 were achieved, limited by catalyst decomposition.

The first well-characterized catalytic alkane dehydrogenation system was reported by Crabtree [10, 11]. $\text{L}_2\text{IrH}_2(\kappa^2\text{-O}_2\text{CCF}_3)$ was found to catalyze dehydrogenation of cycloalkanes and, somewhat less effectively, *n*-alkanes. It was found that dehydrogenation could be catalyzed either by use of a sacrificial hydrogen acceptor or by driving the reaction photochemically. Catalyst deactivation was a critical issue in this and both prior and subsequent alkane dehydrogenation systems; deactivation in this case was demonstrated to occur by P–C hydrogenolysis of the PR_3 ligand [10, 11]. Isotope effects and the isolation of the benzene C–H addition product $\text{L}_2\text{Ir(Ph)(H)(O}_2\text{CCF}_3)$ provided the first strong support for an oxidative addition pathway. This report made explicit the importance of carboxylate dechelation, to yield a three-coordinate d^8 unit after transfer of the H atoms. Virtually all other systems described in this chapter are also based upon three-coordinate d^8 fragments, and in particular, the ML_2X unit, where $\text{M} = \text{Rh}$ or Ir , and X is a halide or anionic group.

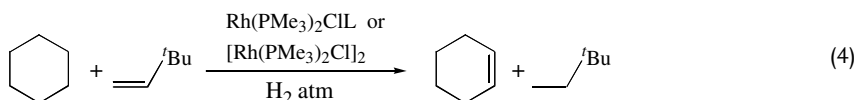
Saito found that Wilkinson’s Catalyst and related rhodium complexes could catalyze dehydrogenation in the absence of acceptor, thermochemically, when H_2 is driven off by reflux, albeit with low turnover numbers [12]. Shortly thereafter, Aoki and Crabtree generalized this reaction; they reported, inter alia, that L_2WH_6 cata-

lyzed acceptorless dehydrogenation, the first example of homogeneous alkane dehydrogenation catalyzed (with or without acceptor) by a non-platinum-group metal [13].

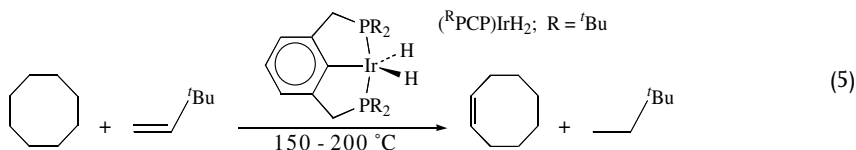
$\text{Rh}(\text{PMe}_3)_2(\text{CO})\text{Cl}$, reported by Tanaka to catalyze alkane photocarbonylation [14], was found to catalyze photodehydrogenation of alkanes to give alkenes in the absence of CO (e.g. Eq. 3) [15–17]. Turnover numbers were quite high (up to 5000), and this reaction might be considered the first example of highly efficient alkane functionalization catalyzed via an organometallic route.



Mechanistic studies of this system led Maguire and Goldman to the conclusion that the role of the photon was expulsion of CO (and not photoelimination of H_2 from an intermediate). The resulting $\text{Rh}(\text{PMe}_3)_2\text{Cl}$ fragment then reacts *thermochemically* with alkane to give $\text{H}_2\text{Rh}(\text{PMe}_3)_2\text{Cl}$; CO then displaces H_2 to complete the catalytic cycle [17]. This implied that this robust fragment offered great potential as a catalyst for thermochemical transfer-dehydrogenation. Attempts to generate thermochemical precursors of $\text{Rh}(\text{PMe}_3)_2\text{Cl}$ in the absence of a strongly binding ligand like CO led only to formation of an inactive dimer. It was found, however, that dihydrogen could react with either monomeric or dimeric species to enter the catalytic cycle via $\text{H}_2\text{Rh}(\text{PMe}_3)_2\text{Cl}$ [18]. The result, surprisingly, is transfer dehydrogenation co-catalyzed by dihydrogen (e.g. Eq. 4).



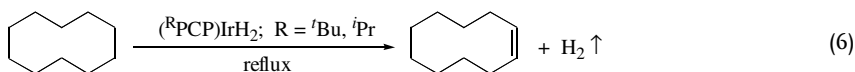
Although the system shown in Eq. (4) gave excellent rates and turnover numbers, the presence of a hydrogen atmosphere led to the hydrogenation of more than one mol acceptor per mol dehydrogenated product. In an effort to circumvent the need for hydrogen, related complexes that would not dimerize were investigated, including pincer complexes containing the unit $(\text{PCP})\text{Rh}$ [19]. These were found to be very poor catalysts; independently, however, Jensen and Kaska found that the iridium analogues gave excellent results for cycloalkane dehydrogenation, particularly at elevated temperatures (Eq. 5) [20].



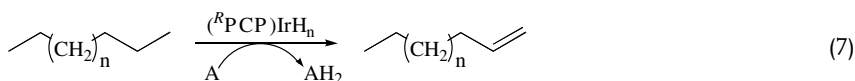
Thus, precursors of $(^{\text{R}}\text{PCP})\text{Ir}$ and $\text{Rh}(\text{PR}_3)_2\text{Cl}$ gave excellent catalysts, in contrast with the “converse” pair, $(^{\text{R}}\text{PCP})\text{Rh}$ and $\text{Ir}(\text{PR}_3)_2\text{Cl}$. Calculations (DFT) by Krogh-Jespersen [21] indicated that this surprising relationship was related to the respective M–H bond strengths of the fragments. Addition of H–H to the model

fragments $\text{Rh}(\text{PH}_3)_2\text{Cl}$ and $\text{Ir}(\text{PH}_3)_2\text{Ph}$ was calculated to be comparably exothermic, by ca. 28 kcal mol^{-1} ; this value is consistent with the alkane-to-metal/metal-to-alkene hydrogen transfers being approximately thermoneutral. In contrast, the enthalpies of addition to the “converse” pair, $\text{Ir}(\text{PH}_3)_2\text{Cl}$ and $\text{Rh}(\text{PH}_3)_2\text{Ph}$, were calculated to be much greater and much smaller, respectively.

The stability of $(^{\text{tBu}}\text{PCP})\text{IrH}_n$ at high temperature was exploited to give rates and turnover numbers for acceptorless dehydrogenation greater than those achieved with any previous catalysts [21].



The $^{\text{iPr}}\text{PCP}$ derivative gave rates and total turnover that were still higher [22]; more importantly, this complex was found to catalyze the selective dehydrogenation of *n*-alkanes to give α -olefins [23].

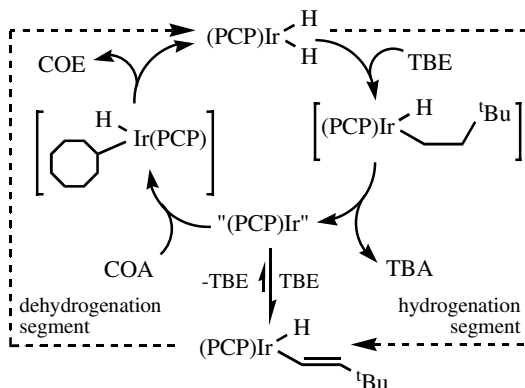


Although the $^{\text{iPr}}\text{PCP}$ complex seemed to afford greater regioselectivity than the $^{\text{tBu}}\text{PCP}$ complex, it was, in fact, found that very high kinetic selectivity for α -olefins was obtained with both complexes [23]. Because of more rapid isomerization relative to dehydrogenation, however, the build-up of α -olefin tended to be lower with the $^{\text{tBu}}\text{PCP}$ complex, although this was found to be highly dependent on reaction conditions.

The presence of electron-donating groups on the pincer aryl ring seems to confer increased stability and, occasionally, increased catalytic activity. Brookhart has found that the bis-phosphinite complexes, $[\kappa^3\text{-}2,6\text{-C}_6\text{H}_3(\text{OP}^{\text{tBu}})_2]\text{IrH}_n$, give turnover frequencies for COA/TBE transfer-dehydrogenation greater than those of the PCP phosphine analog [24]. Although the bis-phosphinite might be expected to be more electron-poor than the bis-phosphine, calculations reveal that the effect of the O-for- CH_2 substitution is primarily due to increased electron-donation to the aryl ring, as for a PCP complex with an (electron-donating) para-methoxy substituent [25].

Mechanistic studies on the $(^{\text{tBu}}\text{PCP})\text{IrH}_n$ -catalyzed COA/TBE transfer-dehydrogenation system were conducted in which the “individual segments” of the cycle were studied stoichiometrically; catalytic and stoichiometric kinetics were then found to be in agreement according to the mechanism in Scheme 1. It was found that the rate-determining segment of the cycle, below ca. 0.2 M [TBE], was the hydrogenation of TBE (Scheme 1) [26]. At higher [TBE] however, the major resting state is the product of TBE vinylic C–H addition to $(^{\text{tBu}}\text{PCP})\text{Ir}$. The rate-determining segment under those conditions includes vinylic C–H elimination and COA dehydrogenation by $(^{\text{tBu}}\text{PCP})\text{Ir}$. Within that segment it seems that C–H addition may be the rate-determining step. It must, however, be mentioned that in many other systems, β -hydrogen elimination is apparently rate-determining. Indeed,

there seems to be a very close balance between barriers to β -H elimination and C–H addition in the (PCP)Ir system; β -H elimination may well be rate-determining with substrates other than COA, and with derivatives other than (^tBuPCP)Ir.



Scheme 1. Mechanism of (PCP)Ir-catalyzed COA/TBE transfer-dehydrogenation.

2.8.2

Substrates Other than Simple Alkanes

The dehydrogenation of highly functionalized organic molecules is beyond the scope of this chapter. The highly regioselective dehydrogenation of complex molecules has been elegantly accomplished by use of tethered ligands constructed for this purpose [27]. More closely related to the subject of this chapter, a small number of examples have been reported in which untethered catalysts effect the selective dehydrogenation of ethylene ($-\text{CH}_2-\text{CH}_2-$) groups of molecules other than simple alkanes.

The dehydrogenation of polyolefins has great potential in the synthesis of functionalized polymers; the connection to alkane dehydrogenation is obvious. Coates and Goldman have reported that poly-1-hexene is transfer-dehydrogenated by (ⁱPrPCP)IrH_n with yields (based on C6-units) up to 18% [28]. In accord with the reactivity with *n*-alkanes, the kinetic products are dehydrogenated at terminal positions of the branches; no evidence of dehydrogenation of the backbone was observed. Linear polyethylene was also dehydrogenated, but with lower yield. Importantly, in both cases the molecular weight distribution of the product indicates the complete absence of any chain scission as a side-reaction accompanying the dehydrogenation.

Jensen has reported that secondary amines are transfer-dehydrogenated by (^tBuPCP)IrH_n to give imines [29]. Lacking an N–H bond, tertiary amines undergo surprisingly facile dehydrogenation with high selectivity to give enamines. This method is particularly effective with *N*-ethyl amines, to give vinyl amines, and is therefore complementary to existing approaches to enamines, because the unsubstituted vinyl amines are particularly difficult to access by conventional routes [30].

Attempts to dehydrogenate ketones have been plagued by product inhibition, particularly by cyclometallation of the initially produced α,β -unsaturated ketones or by additions of aromatized cyclic ketones. Within the range of substrates that is presently very limited by these factors, however, regioselective dehydrogenation of ketones has been successfully achieved [31].

Experimental

Synthesis of (PCP)Ir(H)(Cl)

The method of Moulton and Shaw [32] was modified as follows. [IrCl(cyclooctadiene)]₂ (1.01 g) was added to 1.18 g (3 mmol) of the PCP ligand in toluene at room temperature. This mixture was heated under reflux for 72 h with stirring under an argon atmosphere and the solvent was removed under vacuum. The resulting solid was subjected to Soxhlet extraction with hexane (100 mL). The orange-red hexane solution was concentrated and crystallization from hexane gave 1.74 g (93 %) of the complex as dark red crystals. ³¹P{¹H} NMR (C₆D₆): 67.32 (d, *J*_{HP} = 12.4 Hz). ¹H NMR (C₆D₆): 7.02 (d, *J*_{HH} = 7.6 Hz, 2H), 6.94 (t, *J*_{HH} = 7.6 Hz, 1H), 3.10 (d of vt, *J*_{PH} = 3.8 Hz, *J*_{HH} = 17.3 Hz, 2H, CH₂), 2.00 (d of vt, *J*_{PH} = 3.8 Hz, *J*_{HH} = 17.3 Hz, 2H, CH₂), 1.27 (t, *J*_{PH} = 6.4 Hz, 18 H, C(CH₃)₃), 1.22 (t, *J*_{PH} = 6.4 Hz, 18H, C(CH₃)₃), -42.6 (t, *J*_{PH} = 12.6 Hz, 1H).

Synthesis of (PCP)IrH_n

A modification of the method of Kaska and Jensen was used [20]. A solution of (PCP)Ir(H)(Cl) (0.40 g, 0.64 mmol) in 150 mL pentane was saturated with H₂ at room temperature. To this solution was added, dropwise, 0.64 mL of 1 M LiBEt₃H in THF (0.64 mmol) while H₂ was bubbled through solution. The solution turned lighter in color and some white precipitate was formed. Addition of LiBEt₃H was stopped when the solution became yellow. The solution was filtered and the solvent removed in vacuo to give 0.34 g (90 %) of a red-brown mixture of the dihydride and the tetrahydride. ³¹P{¹H} NMR (C₆D₆): (PCP)IrH₂: 86.14(s), (PCP)IrH₄: 73.08 (s). ¹H NMR (C₆D₆): (PCP)IrH₂: 7.4 (d, *J*_{HH} = 7.2 Hz, 2H), 7.26 (t, *J*_{HH} = 7.2 Hz, 1H), 3.54 (br s, 4H), 1.23 (t, *J*_{PH} = 6.4 Hz, 36 H), -19.2 (t, *J*_{PH} = 8.8 Hz, 2H). (PCP)IrH₄: 7.4 (d, *J*_{HH} = 7.2 Hz, 2H), 7.26 (t, *J*_{HH} = 7.2 Hz, 1H), 3.29 (t, *J*_{PH} = 3.6 Hz, 4H), 1.18 (t, *J*_{PH} = 6.4 Hz, 36 H), -9.1 (t, *J*_{PH} = 9.6 Hz, 4 H). Pure tetrahydride can be generated by subsequent addition of hydrogen atmosphere whereas pure dihydride can be generated by repeated dissolution in toluene and removal of the solvent in vacuo; for catalysis, however, the dihydride/tetrahydride mixture is satisfactory. The synthesis of (MeO-^RPCP)IrH_n (R = *t*-Bu or *i*-Pr) has been described elsewhere [25].

Transfer Dehydrogenation

Alkane/NBE transfer dehydrogenation experiments were typically conducted as follows. In an argon-atmosphere glovebox, 0.5 mL alkane solution (15 mM catalyst, and NBE) was placed in a 5-mL reactor. The reactor was fitted with a Kontes high-vacuum stopcock, which enables freeze-pump-thaw cycles and addition of argon,

and with an Ace Glass “Adjustable Electrode Ace-Thred Adapter” which enables removal of 0.5- μ L samples. The charged apparatus was removed from the glovebox and additional argon was added on a vacuum-line to give a total pressure of 800 torr. The reactor was put into a GC oven at the desired temperature. Samples were periodically taken by means of a microliter syringe for GC analysis. After monitoring of the reactions in this manner, the apparatus was typically returned to the glovebox where the solution was transferred to an NMR tube. ^1H NMR was used to confirm the identity and approximate concentration of the products.

2.9

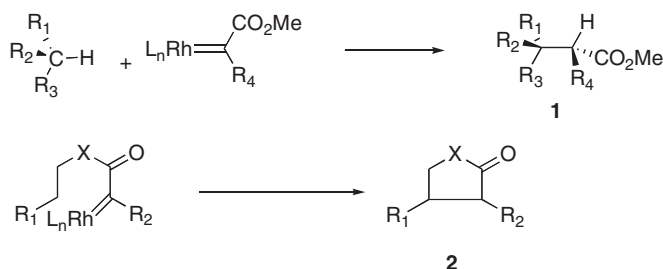
Rhodium-catalyzed Enantioselective Carbene Addition

Huw M.L. Davies

2.9.1

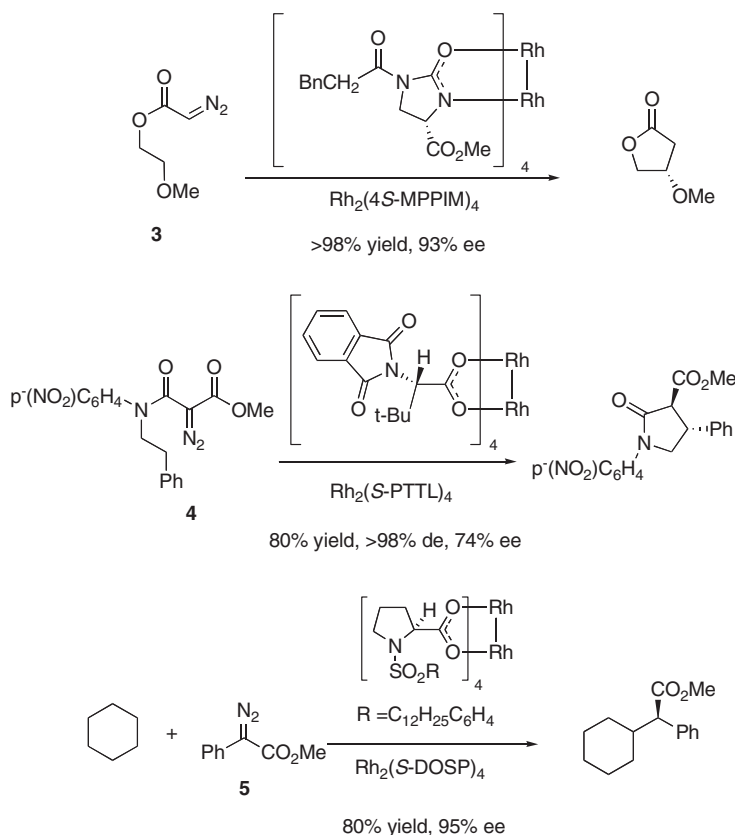
Introduction and Fundamental Examples

The C–H insertion chemistry of metal carbenoids is a very general method for selective transformation of C–H bonds [1]. The metal carbenoids are readily generated by metal-catalyzed decomposition of diazo compounds and they induce a wide range of highly regioselective and stereoselective C–H transformations as shown in the generic reactions producing **1** and **2** (Scheme 1). Even though inter- and intramolecular examples of this reaction have been known for over 30 years, the intermolecular version has only recently been recognized as synthetically useful, because of the development of highly chemoselective donor–acceptor substituted rhodium carbenoids [1c]. Many recent reviews have been published on this C–H insertion chemistry [1]. This overview will summarize the reactivity of these metal carbenoids, with emphasis on enantioselective C–H transformations.



Scheme 1. Intermolecular and intramolecular C–H insertions.

Both inter- and intramolecular C–H insertions can be achieved with high asymmetric induction and they have been applied to the enantioselective synthesis of many natural products and pharmaceutical agents [1]. Five-membered rings are most commonly formed in intramolecular reactions, although by judicious choice of substrates and catalysts four and six membered and even larger rings may also



Scheme 2. Specific examples of intermolecular and intramolecular C–H insertions.

be formed. Over the last few years, the enantioselective intermolecular reaction has been shown to be of broad scope [1c]. Several chiral catalysts have been applied to this chemistry [1], but overall the most widely applied catalysts are dirhodium complexes illustrated in Scheme 2. Dirhodium carboxamidates such as $\text{Rh}_2(4S\text{-MPPIM})_4$ are best for carbenoid precursors **3** with a single acceptor substituent [2]. The phthalimido amino acid derivatives such as $\text{Rh}_2(S\text{-PTLL})_4$ are best for doubly acceptor-substituted carbenoid precursors **4** [3] whereas dirhodium tetraprolinates such as $\text{Rh}_2(S\text{-DOSP})_4$ are best for donor/acceptor substituted carbenoid precursors **5** [4]. Several variations of these three types of catalysts have been prepared, which broadens the range of highly enantioselective C–H insertions and enables substantial regiocontrol [1].

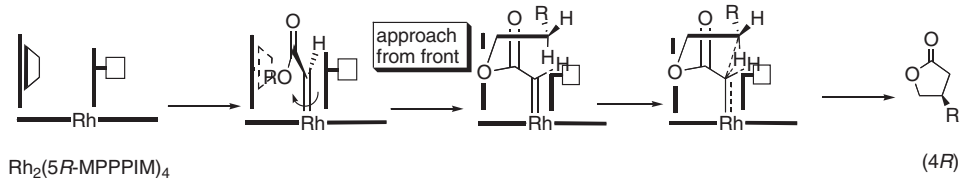
2.9.2

Mechanism

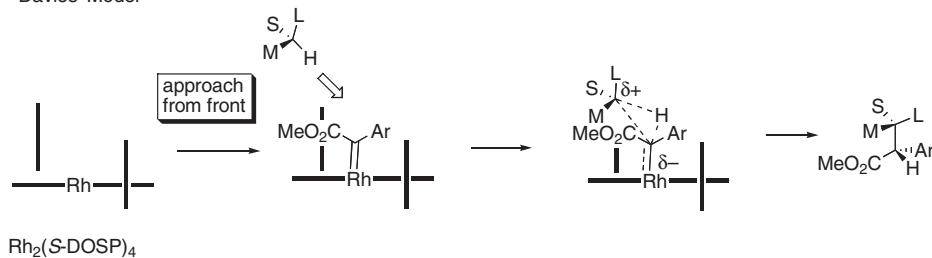
The mechanism of these C–H insertion reactions and the rhodium carbenoid reactions in general are still a matter of considerable debate [1]. It is generally

agreed that the first step, metal-catalyzed decomposition of the diazo compound to a metal carbenoid, is followed by C–H insertion. Several models have been developed to rationalize the exquisite stereoselectivity exhibited in this chemistry and these models have excellent predictive power for both relative and absolute stereochemistry of the C–H insertions [4, 6]. Most of the models have assumed the dirhodium tetraligand core remains intact, but even this has been questioned recently, and it has been suggested that ligand dissociation occurs on carbene coordination [5]. If the dirhodium complex remains intact then C–H insertion would need to occur away from the metal and the metal does not play a role in the C–H activation, because it would already be coordinatively saturated. Thus, the stereochemical outcome would be highly dependent on the trajectory of the approach of the carbenoid. The early predictive models rely on either a side-on [4] or an end-on approach [6a, b] of the substrates. This is illustrated for Doyle's model for intramolecular C–H insertion of diazoacetates [6a] and for Davies' model for intermolecular C–H insertions of aryldiazoacetates [4] (Scheme 3). Recent theoretical calculations on intermolecular C–H insertions of diazoacetate favor an end-on approach of the substrate to the carbenoid [7]. As computational studies become more advanced and the structure of the rhodium carbenoids becomes better defined, it is very likely that mechanistic understanding of this chemistry will evolve and become much more sophisticated. If ligand dissociation does, indeed, occur on carbene coordination [5], it is probable that the C–H insertion process would have a C–H activation component to its mechanism.

Doyle's Model



Davies' Model

**Scheme 3.** Predictive mechanistic models for C–H insertion.

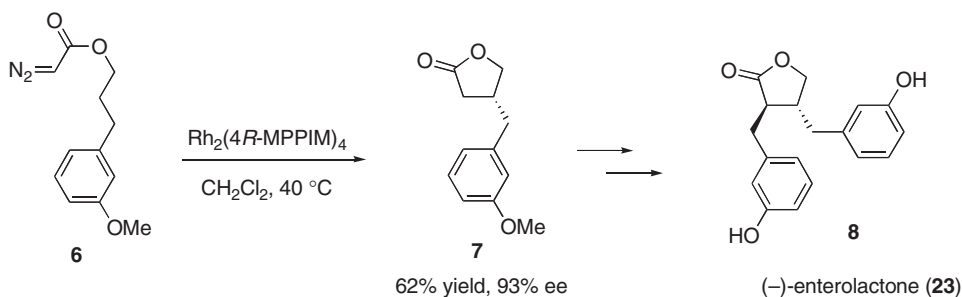
2.9.3

Scope and Limitations

2.9.3.1 Intramolecular Reactions

The enantioselective intramolecular C–H insertion is a very general synthetic process [1]. The C–H insertion can occur on methyl, methylene and methine sites, but often excellent regiocontrol is achieved by means of the appropriate substrate and tether. Electron-donating groups adjacent to the C–H bond favor C–H insertion whereas electron withdrawing groups disfavor the reaction. A comprehensive review describing the full scope of this chemistry has recently been published [1c]. Only a few representative examples will be discussed here.

The enantioselective intramolecular C–H insertion of alkyl diazoacetates has been used to prepare a variety of pharmaceutical and natural products [1]. One example is the synthesis of (–)-enterolactone (**8**) shown in Scheme 4 [2]. The $\text{Rh}_2(4S\text{-MPPIM})_4$ -catalyzed reaction of **6** favors C–H insertion to form the γ -lactone **7** in 93 % ee, which was the readily converted to **8**. Competing C–H insertion at the highly activated benzylic C–H bond to form a β -lactone was not observed, which illustrates the strong preference for five-membered ring formation over six-membered.

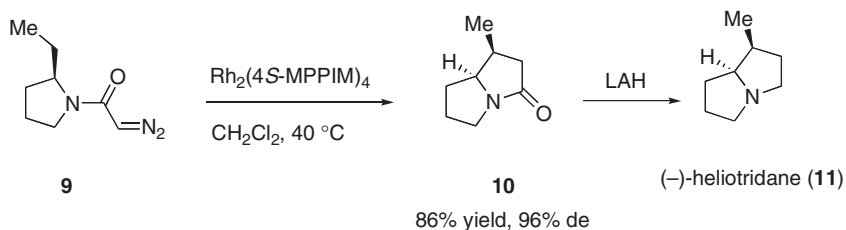


Scheme 4. $\text{Rh}_2(4S\text{-MPPIM})_4$ catalyzed intramolecular C–H insertion of an alkyl diazoacetate.

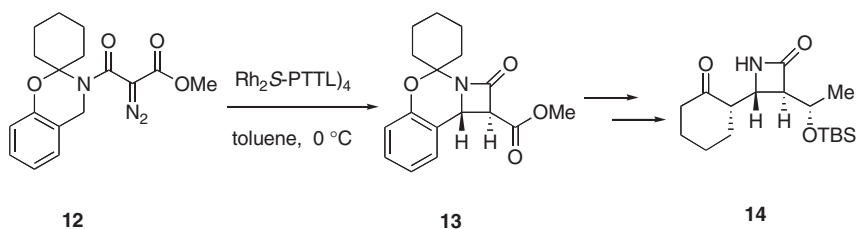
Diazoacetamides are also exceptional substrates for dirhodium carboxamidate-catalyzed reactions, although with these substrates a mixture of β -lactam and γ -lactam products are formed [8]. The rhodium carboxamidate catalyst can have a major effect on the ratio of products formed. A good synthetic example is the $\text{Rh}_2(4S\text{-MPPIM})_4$ -catalyzed synthesis of (–)-heliotridane **11** (Scheme 5) [9]. The key C–H insertion step of **9** generated the indolizidine **10** in 86 % yield and 96 % de, whereas reaction of **9** with achiral catalysts tended to favor the opposite diastereomer.

The reaction of α -methoxycarbonyl- α -diazoacetamides is best catalyzed by $\text{Rh}_2(\text{S-PTTL})_4$ or related catalysts [2, 10]. Again, there is competition between β -lactam and γ -lactam formation. The chemistry has been applied to the synthesis of a variety of β -lactam derivatives, as illustrated in Scheme 6 [11]. $\text{Rh}_2(\text{S-PTTL})_4$ -cata-

lyzed decomposition of **12** results in the highly diastereoselective formation of the β -lactam **13** in 84 % ee, which was then readily converted to the key pharmaceutical precursor **14**.

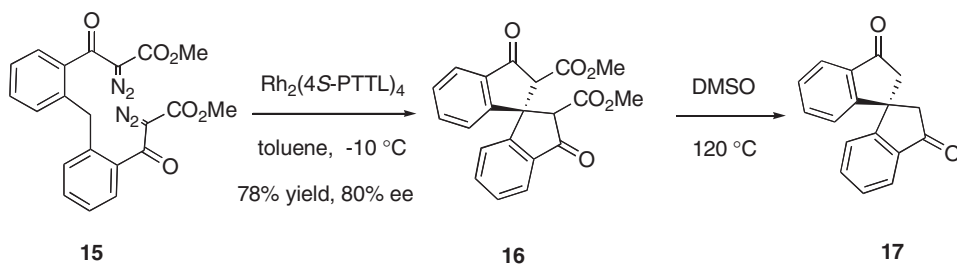


Scheme 5. $\text{Rh}_2(4\text{S-MPPIM})_4$ catalyzed intramolecular C–H insertion of an alkyl diazoacetamide.



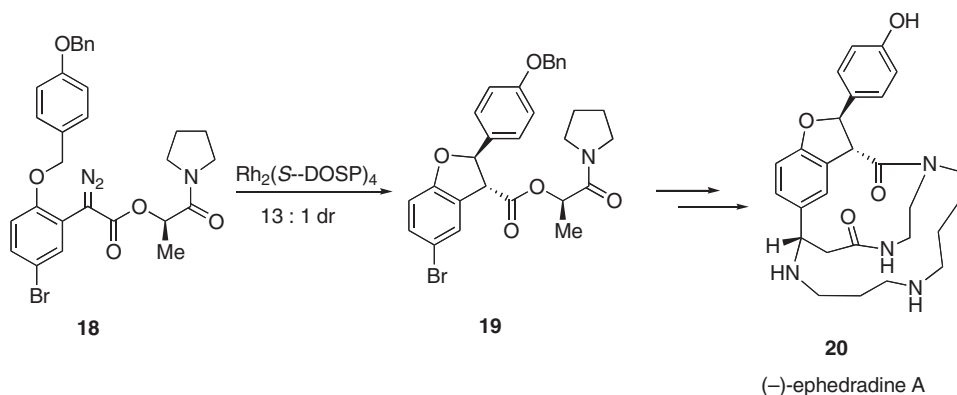
Scheme 6. $\text{Rh}_2(\text{S-PTTL})_4$ catalyzed intramolecular C–H insertion of an α -methoxycarbonyl- α -diazoacetamide.

A more elaborate example involving a diazoacetate derivative (**15**) is the double C–H insertion to form **16**[12]. Decarboxylation of **16** generates the spiro compound **17** in 80 % ee.



Scheme 7. $\text{Rh}_2(\text{S-PTTL})_4$ catalyzed double C–H insertion.

Intramolecular C–H insertions of aryldiazoacetates have been effectively achieved with high asymmetric induction by using either $\text{Rh}_2(\text{S-DOSP})_4$ [13] or $\text{Rh}_2(\text{S-PTTL})_4$ [14] as catalyst. An impressive recent example is a key step (**18** to **19**) in the synthesis of (–)-ephedradine A (**20**) (Scheme 8) [15]. In this particular case, a double stereodifferentiation with a chiral catalyst and auxiliary gave the best asymmetric induction.

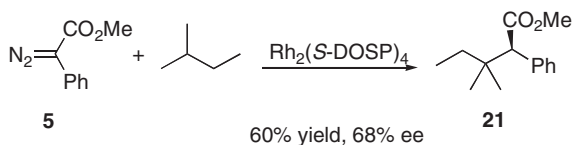


Scheme 8. $\text{Rh}_2(\text{S-DOSP})_4$ -catalyzed intramolecular C–H insertion of an aryldiazoacetate.

2.9.3.2 Intermolecular Reactions

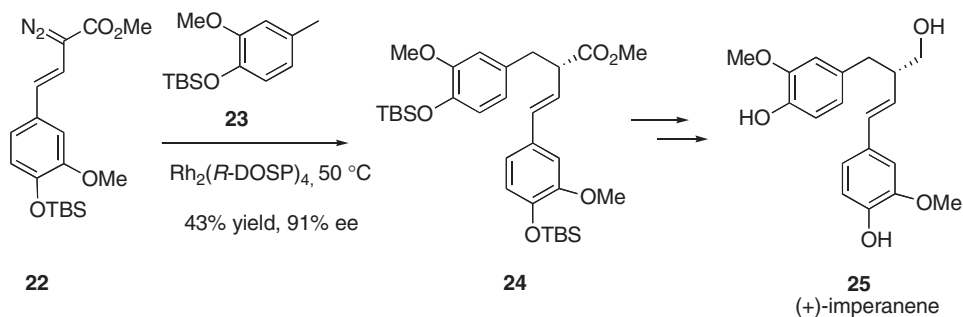
Donor/acceptor-substituted carbenoids are usually much more chemoselective than the more established carbenoids functionalized solely with acceptor groups [1c]. The development of these donor/acceptor-substituted carbenoids has enabled enantioselective intermolecular C–H insertions to become a very practical process. These carbenoids have a strong preference for functionalizing C–H bonds where positive charge build-up at C in the transition state is favored but these electronic effects are counter-balanced by steric factors. Benzylic and allylic sites and C–H bonds adjacent to oxygen and nitrogen functionality are favored but these sites can also be sterically protected if desired. By appropriate consideration of the regiocontrolling elements, effective intermolecular C–H insertions at methyl, methylene, and methine sites have been achieved.

The intermolecular C–H insertion of alkanes is very chemoselective, as is illustrated by the reaction with 2-methylbutane [4]. The only C–H transformation observed occurs at the methine site to form **21** in 68 % ee. This result is very different from the rhodium carboxylate-catalyzed reactions of ethyl diazoacetate with 2-methylbutane, which gives rise to all four C–H insertion products [16]. Improved regioselectivity has recently been achieved in the intermolecular C–H insertion chemistry of ethyl diazoacetate by using either copper [17] or silver [18] scorpionate catalysts, but enantioselective versions of these reactions are not known.



Scheme 9. C–H transformation of 2-methylbutane.

Although a range of alkanes have been functionalized by the carbenoid-induced insertion, much more synthetically useful reactions have been achieved in systems which are more activated. Benzylic C–H insertions have been widely explored and offer a new strategic reaction for synthesis [19]. A very elegant example is the short enantioselective synthesis of imperanene (**25**) shown in scheme 10 [20]. With donor/acceptor substituted carbenoids, aromatic rings are sterically protected as long as they are at least 1,4-disubstituted. Thus, even though both aromatic rings in **22** and **23** are very electron-rich, they are still compatible with the C–H insertion chemistry and the $\text{Rh}_2(\text{S-DOSP})_4$ (1 mole %) catalyzed reaction of **22** with **23** generates **24** in 91 % ee.



Scheme 10. Benzylic C–H transformation.

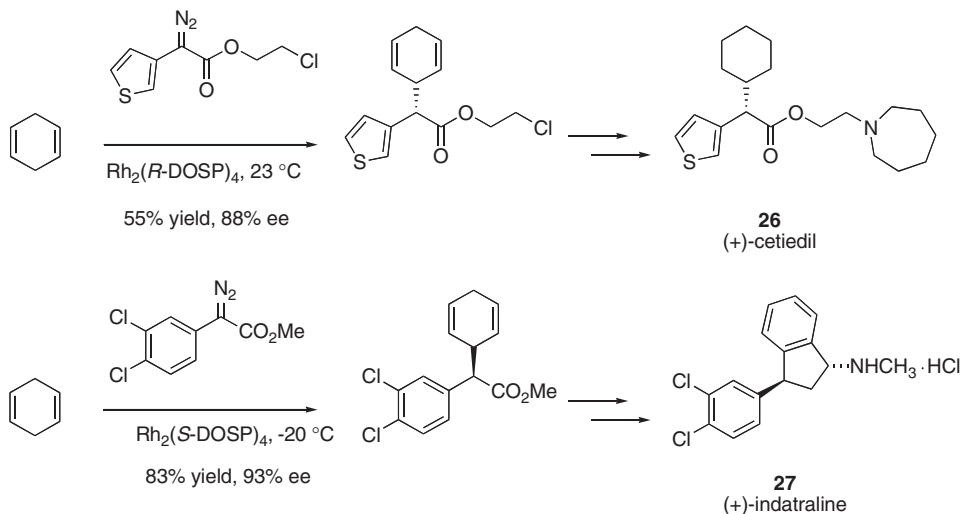
Allylic C–H insertions have been used in key steps of the enantioselective synthesis of the pharmaceuticals (+)-ceitedil (**26**) [21] and (+)-indatraline (**27**) [22] (Scheme 11). The allylic C–H insertion reaction is an exciting alternative to the Claisen rearrangement as a rapid method for the synthesis of γ,δ -unsaturated ester [23]. Similarly, the allylic C–H insertion with vinyl silyl ethers generates protected 1,5-dicarbonyl compounds, a complimentary reaction to the Michael addition [24]. Both types of C–H insertion can be achieved with high diastereoselectivity and enantioselectivity [23, 24].

C–H activation adjacent to oxygen is an excellent method for synthesis of protected β -hydroxy esters and can be regarded as a synthetic equivalent to an aldol reaction. An example showing the highly regioselective and diastereoselective nature of this reaction is shown in Scheme 12 [25]. The (*E,E*)-diene in **28** is sterically protected and the acetoxy group is inductively strongly electron-withdrawing. Consequently, the C–H insertion occurs preferentially α to the O-silyl group to form **29** in 92 % yield.

The intermolecular C–H insertion on *N*-Boc-piperidine leads to the rapid access of the pharmaceutical agent *threo*-methylphenidate (**30**) [26]. As this reaction is of commercial interest, a range of chiral catalysts have been examined [26]. The best enantioselectivity was obtained with $\text{Rh}_2(\text{S-biDOSP})_2$, which is a bridged second generation analog of $\text{Rh}_2(\text{S-DOSP})_4$ [26a, b].

The C–H insertion α to nitrogen is also a strategically significant reaction because the resulting β -amino esters would be the typical products of a Mannich

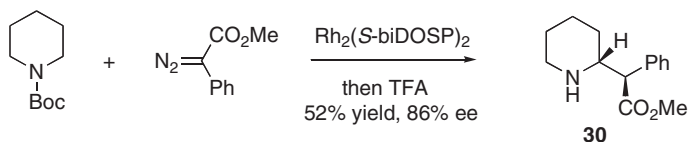
reaction[26c]. The reaction with *N*-Boc-pyrrolidine is highly diastereoselective and, as can be seen in the reaction with the 3-substituted pyrrolidine **31**, exceptionally high kinetic resolution can be achieved using this chemistry, resulting in the formation of **32** in 99 % ee and >94 % de.



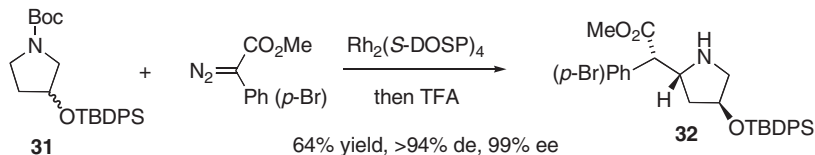
Scheme 11. Allylic C–H transformation.



Scheme 12. C–H transformation as a surrogate to the aldol reaction.

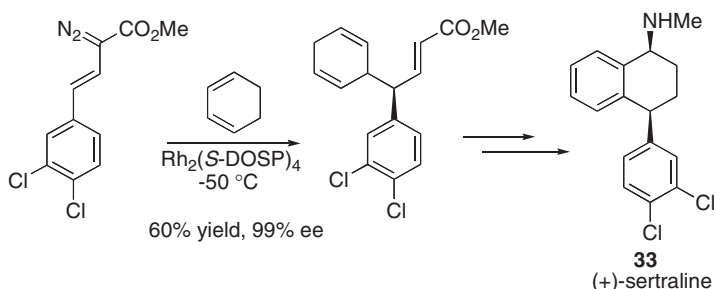


Scheme 13. Enantioselective synthesis of *threo* methylphenidate.



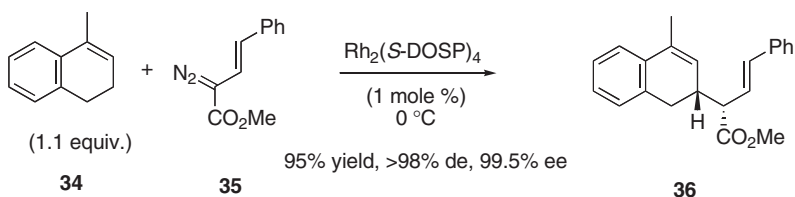
Scheme 14. Kinetic resolution by C–H transformation.

Attempted allylic C–H insertion by vinyl diazoacetates results in an even more complicated transformation, a combined C–H activation/Cope rearrangement [27]. These reactions tend to proceed with very high enantioselectivity as illustrated in a short enantioselective synthesis of the antidepressant (+)-sertraline (**33**) [27a]. Recent studies have shown that this reaction is both highly diastereoselective and enantioselective [27b].



Scheme 15. Combined C–H activation/Cope rearrangement.

One of the most spectacular examples of these C–H transformations involving rhodium carbenoids is the reaction between dihydronaphthalenes and vinyl diazoacetates [28]. As can be seen in Scheme 16, the reaction between the dihydronaphthalene **34** and the vinyl diazoacetate **35**, catalyzed by $\text{Rh}_2(\text{S-DOSP})_4$, generates the formal C–H insertion product **36** in 99.5% ee and >98% de. The yield of **36** is 95% even though the vinyl diazoacetate **35** was used as the limiting reagent. The reaction has been shown to involve a cascade of a combined C–H activation/Cope rearrangement followed by a retro-Cope rearrangement [28].



Scheme 16. C–H transformation of a dihydronaphthalene.

In summary, the C–H insertion chemistry of rhodium carbenoids is a very powerful method for transformation of C–H bonds. Highly regioselective and stereoselective reactions are possible and several classes of chiral catalyst are capable of very high asymmetric induction. The chemoselectivity in this chemistry is exceptional, as illustrated by the numerous intermolecular and intramolecular reactions described in this overview. Most notably, this chemistry offers new and practical strategies for enantioselective synthesis of a variety of natural products and pharmaceutical agents.

Experimental

Methyl α -Cyclohexylbenzeneacetate

A degassed solution of methyl phenyldiazoacetate (**5**) (183 mg, 1.04 mmol) in anhydrous cyclohexane (10 mL) was added dropwise over 90 min to a stirring degassed solution of $\text{Rh}_2(\text{S-DOSP})_4$ (20 mg, 0.01 mmol) in anhydrous cyclohexane (5 mL) at 0 °C. The solution was stirred for a further 15 min at 0 °C. The solvent was then removed in vacuo, and purified by flash chromatography with 2 % Et_2O –pet ether to give the product (194 mg, 80 % yield) as a colorless oil: 95 % ee (Chiralcel OD, FR 1.0 mL min⁻¹, 0.6 % i-propanol–hexane, R_t = 8.6 and 10.4 min, UV 254 nm); $[\alpha]_D^{23}$ = -36.6° (c 1.8, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 7.31–7.22 (m, 5 H), 3.64 (s, 3 H), 3.22 (d, 1 H, J = 10.6 Hz), 2.03–1.97 (m, 1 H), 1.81–1.56 (m, 4 H), 1.32–1.01 (5 H), 0.87–0.70 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 174.4, 137.9, 128.6 (CH), 128.4 (CH), 127.2 (CH), 58.8 (CH), 51.7 (CH_3), 41.0 (CH), 32.0 (CH_2), 30.4 (CH_2), 26.2 (CH_2), 25.94 (CH_2), 25.90 (CH_2); IR (neat): 3028, 2926, 2850, 1735, 1497 cm⁻¹. Anal. calcd for $\text{C}_{15}\text{H}_{20}\text{O}_2$: C, 77.55; H, 8.68. Found: C, 77.47; H, 8.69.

References and Notes to Section 2 – C–H Transformation at Unfunctionalized Alkanes

References and Notes to Section 2.1.1

- 1 P. Stavropoulos, R. Çelenligil-Çetin, A. E. Tapper, *Acc. Chem. Res.* **2001**, *34*, 745–752.
- 2 D. H. R. Barton, D. Doller, *Acc. Chem. Res.* **1992**, *25*, 504–512.
- 3 I. Tabushi, T. Nakajima, K. Seto, *Tetrahedron Lett.* **1980**, *21*, 2565–2568.
- 4 D. H. R. Barton, S. D. Bévière, W. Chavasiri, E. Csuhai, D. Doller, W.-G. Liu, *J. Am. Chem. Soc.* **1992**, *114*, 2147–2156.
- 5 C. A. Tolman, J. D. Druliner, M. J. Nappa, N. Herron, *Alkane Oxidation Studies in D. Pont's Central Research Department*, in: *Activation and Functionalization of Alkanes*, C. L. Hill (Ed.), pages 303–360, Wiley: New York **1989**.
- 6 D. H. R. Barton, B. Hu, D. K. Taylor, R. U. Rojas Wahl, *J. Chem. Soc., Perkin Trans. 2* **1996**, 1031–1041.
- 7 (a) S. Kiani, A. Tapper, R. J. Staples, P. Stavropoulos, *J. Am. Chem. Soc.* **2000**, *122*, 7503–7517; (b) A. E. Tapper, J. R. Long, R. J. Staples, P. Stavropoulos, *Angew. Chem., Int. Ed.* **2000**, *39*, 2343–2346; (c) R. Çelenligil-Çetin, R. J. Staples, P. Stavropoulos, *Inorg. Chem.* **2000**, *39*, 5838–5846; (d) B. Singh, J. R. Long, F. Fabrizi de Biani, D. Gatteschi, P. Stavropoulos, *J. Am. Chem. Soc.* **1997**, *119*, 7030–7047.
- 8 D. H. R. Barton, M. J. Gastiger, W. B. Motherwell, *J. Chem. Soc., Chem. Commun.* **1983**, 41–43.
- 9 D. H. R. Barton, R. S. Hay-Motherwell, W. B. Motherwell, *Tetrahedron Lett.* **1983**, *24*, 1979–1982.
- 10 D. H. R. Barton, J. Boivin, M. Gastiger, J. Morzycki, R. S. Hay-Motherwell, W. B. Motherwell, N. Ozbalik, K. M. Schwartzentruber, *J. Chem. Soc., Perkin Trans.* **1986**, 947–955.
- 11 G. Balavoine, D. H. R. Barton, J. Boivin, A. Gref, N. Ozbalik, H. Rivière, *Tetrahedron Lett.* **1986**, *27*, 2849–2852.
- 12 D. H. R. Barton, F. Halley, N. Ozbalik, E. Young, G. Balavoine, A. Gref, J. Boivin, *New J. Chem.* **1989**, *13*, 177–182.
- 13 D. H. R. Barton, F. Halley, N. Ozbalik, M. Schmitt, E. Young, G. Balavoine, *J. Am. Chem. Soc.* **1989**, *111*, 7144–7149.
- 14 E. About-Jaudet, D. H. R. Barton, E. Csuhai, N. Ozbalik, *Tetrahedron Lett.* **1990**, *31*, 1657–1660.

- 15 D. H. R. Barton, E. Csuhai, D. Doller, Y. V. Geletii, *Tetrahedron* **1991**, *47*, 6561–6570.
- 16 D. H. R. Barton, S. D. Bévière, W. Chavasiri, E. Csuhai, D. Doller, *Tetrahedron* **1992**, *48*, 2895–2910.
- 17 D. H. R. Barton, *Synlett* **1996**, 229–230.
- 18 D. H. R. Barton, *Tetrahedron* **1998**, *54*, 5805–5817.
- 19 C. Knight, M. J. Perkins, *J. Chem. Soc., Chem. Commun.* **1991**, 925–927.
- 20 F. Minisci, F. Fontana, S. Araneo, F. Recupero, L. Zhao, *Synlett* **1996**, 119–125.
- 21 D. W. Snelgrove, P. A. MacFaul, K. U. Ingold, D. D. M. Wayner, *Tetrahedron Lett.* **1996**, *37*, 823–826.
- 22 F. Minisci, F. Fontana, S. Araneo, F. Recupero, S. Banfi, S. Quici, *J. Am. Chem. Soc.* **1995**, *117*, 226–232.
- 23 M. Newcomb, P. A. Simakov, S.-U. Park, *Tetrahedron Lett.* **1996**, *37*, 819–822.
- 24 M. J. Perkins, *Chem. Soc. Rev.* **1996**, 229–236.
- 25 F. Recupero, A. Bravo, H.-R. Bjørsvik, F. Fontana, F. Minisci, M. Piredda, *J. Chem. Soc., Perkin Trans. 2* **1997**, 2399–2405.
- 26 G. A. Russell, *Radical Reactions of Alkanes and Cycloalkanes*, in: *The Chemistry of Alkanes and Cycloalkanes*, S. Patai, Z. Rappoport (Eds.), pages 963–997, Wiley: New York **1992**.
- 27 G. V. Buxton, C. L. Greenstock, W. P. Helman, A. B. Ross, *J. Phys. Chem. Ref. Data* **1988**, *17*, 513–886.
- 28 K. G. Konya, T. Paul, S. Lin, J. Luszyk, K. U. Ingold, *J. Am. Chem. Soc.* **2000**, *122*, 7518–7527.
- 29 S. B. Marr, R. O. Carvel, D. T. Richens, H.-J. Lee, M. Lane, P. Stavropoulos, *Inorg. Chem.* **2000**, *39*, 4630–4638.
- 30 (a) C. Walling, *Acc. Chem. Res.* **1998**, *31*, 155–157; (b) C. Walling, *Acc. Chem. Res.* **1975**, *8*, 125–131.
- 31 G. A. Russell, *J. Am. Chem. Soc.* **1957**, *79*, 3871–3877.
- 32 B. Giese, *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*, Pergamon Press: Oxford **1986**.
- 33 See articles in thematic issue: *Radical Enzymol*, *Chem. Rev.* June **2003**.
- 34 U. Schuchardt, W. A. Carvalho, E. V. Spinacé, *Synlett* **1993**, 713–718.
- 35 A. T. Nielsen, D. W. Moore, G. M. Muha, K. Highberg Berry, *J. Org. Chem.* **1964**, *29*, 2175–2179.
- 36 U. S. Schubert, C. Eschbaumer, M. Heller, *Org. Lett.* **2000**, *2*, 3373–3376.
- 37 B. Heller, B. Sundermann, H. Buschmann, H.-J. Drexler, J. You, U. Holzgrabe, E. Heller, G. Oehme, *J. Org. Chem.* **2002**, *67*, 4414–4422.
- 38 F. Minisci, E. Vismara, F. Fontana, *Heterocycles* **1989**, *28*, 489–519.
- 39 F. Fontana, F. Minisci, E. Vismara, *Tetrahedron Lett.* **1988**, *29*, 1975–1978.

References and Notes for Section 2.1.2

- 1 W. Adam, F. Heckel, C. R. Saha-Möller, P. Schreier, *J. Organomet. Chem.* **2002**, *661*, 17.
- 2 S. J. Lange, L. Que, *Curr. Opinion Chem. Biol.* **1998**, *2*, 159.
- 3 J. O. Edwards, R. H. Pater, R. Curci, F. D. Furia, *Photochem. Photobiol.*, **1979**, *30*, 63.
- 4 R. W. Murray, R. Jeyaraman, *J. Org. Chem.* **1985**, *50*, 2847.
- 5 W. Adam, C.-G. Zhao, In *The Chemistry of Peroxides*, S. Patai, Z. Rappoport Eds.; Wiley-VCH, in press.
- 6 W. Adam, C. R. Saha-Möller, C.-G. Zhao, *Org. React.*, **2002**, *61*, 219.
- 7 M. Frohn, Y. Shi, *Synthesis*, **2000**, 1979.
- 8 W. Adam, H.-G. Degen, A. Pastor, C. R. Saha-Möller, S. B. Schambony, C.-G. Zhao, In *Peroxide Chemistry: Mechanistic and Preparative Aspects of Oxygen Transfer*, W. Adam Ed.; Wiley-VCH: Weinheim, **2000**, pp. 78–112.
- 9 S. E. Denmark, Z. Wu, *Synlett*, **1999**, 847.
- 10 W. Adam, A. K. Smerz, C.-G. Zhao, *J. Prakt. Chem.*, **1997**, *339*, 298.
- 11 R. W. Murray, M. Singh, In *Comprehensive Heterocyclic Chemistry II*; A. Padwa, Ed.; Elsevier: Oxford, **1996**, Vol. 1A; pp. 429–456.
- 12 W. Adam, A. K. Smerz, *Bull. Soc. Chim. Belg.*, **1996**, *105*, 581.
- 13 A. Lévai, W. Adam, J. C. Halász, C. Nemes, T. Patonay, G. Tóth, *Chem. Heterocycl. Compd. (UDSSR) (Engl. Trans.)*, **1995**, *10*, 1345.

- 14 R. Curci, A. Dinoi, M. F. Rubino, *Pure Appl. Chem.*, **1995**, 67, 811.
- 15 W. Adam, L. Hadjiarapoglou, *Top. Curr. Chem.*, **1993**, 164, 45.
- 16 W. Adam, L. P. Hadjiarapoglou, R. Curci, R. Mello, In *Organic Peroxides*; W. Ando Ed.; Wiley: New York, 1992, Chapter 4; pp. 195–219.
- 17 R. Curci, In *Advances in Oxygenated Process*; A. L. Baumstark Ed.; JAI: Greenwich CT, 1990, Vol. 2, Chapter I; pp. 1–59.
- 18 W. Adam, R. Curci, J. O. Edwards, *Acc. Chem. Res.*, **1989**, 22, 205.
- 19 R. W. Murray, *Chem. Rev.*, **1989**, 89, 1187.
- 20 R. W. Murray, R. Jeyaraman, L. Mohan, *J. Am. Chem. Soc.* **1986**, 108, 2470.
- 21 W. Adam, R. Curci, L. D'Accolti, A. Dinoi, C. Fusco, F. Gasparrini, R. Kluge, R. Paredes, M. Schulz, A. K. Smerz, L. A. Veloz, S.; Weinkötz, R. Winde, *Chem. Eur. J.* **1997**, 3, 105.
- 22 W. Adam, G. Asensio, R. Curci, M. E. González-Núñez, R. Mello, *J. Org. Chem.* **1992**, 57, 953.
- 23 G. Asensio, R. Mello, M. E. González-Núñez, G. Castellano, J. Corral, *Angew. Chem., Intl. Ed. Engl.* **1996**, 35, 217.
- 24 R. Mello, M. Fiorentino, C. Fusco, R. Curci, *J. Am. Chem. Soc.* **1989**, 111, 6749.
- 25 P. Bovicelli, P. Lupatelli, V. Fiorini, E. Mincione, *Tetrahedron Lett.* **1993**, 34, 6103.
- 26 B. Voigt, A. Porzel, D. Golsch, W. Adam, G. Adam, *Tetrahedron* **1996**, 52, 10653.
- 27 W. Adam, C. R. Saha-Möller, C.-G. Zhao, *Tetrahedron, Asymmetry* **1998**, 9, 4117.
- 28 W. Adam, C. R. Saha-Möller, C.-G. Zhao, *J. Org. Chem.* **1999**, 64, 7492.
- 29 R. Mello, L. Cassidei, M. Fiorentino, C. Fusco, W. Hümmer, V. Jäger, R. Curci, *J. Am. Chem. Soc.* **1991**, 113, 2205.
- 30 M. N. Glukhovtsev, C. Canepa, R. D. Bach, *J. Am. Chem. Soc.* **1998**, 120, 10528.
- 31 K. N. Houk, X. Du, *J. Org. Chem.* **1998**, 63, 6480.
- 32 G. V. Shustov, A. Rauk, *J. Org. Chem.* **1998**, 63, 5413.
- 33 R. Curci, A. Dinoi, C. Fusco, M. A. Lillo, *Tetrahedron Lett.* **1996**, 37, 249.
- 34 F. Minisci, L. Zhao, F. Fontana, A. Bravo, *Tetrahedron Lett.*, **1995**, 36, 1895.
- 35 A. Bravo, F. Fontana, G. Fronza, F. Minisci, L. Zhao, *J. Org. Chem.*, **1998**, 63, 254.
- 36 W. Adam, R. Curci, L. D'Accolti, A. Dinoi, C. Fusco, F. Gasparrini, R. Kluge, R. Paredes, M. Schulz, A. K. Smerz, L. A. Veloz, S.; Weinkötz and R. Winde, *Chem. Eur. J.*, **1997**, 3, 105.
- 37 Curci, L. D'Accolti, M. Fiorentino, C. Fusco, W. Adam, M. E. González-Núñez, R. Mello, *Tetrahedron Lett.*, **1992**, 33, 4225.
- 38 R. W. Murray, M. Singh, R. Jeyaraman, *J. Am. Chem. Soc.* **1992**, 114, 1346.
- 39 M. Gilbert, M. Ferrer, F. Sánchez-Baeza, A. Messeguer, *Tetrahedron* **1997**, 53, 8643.
- 40 W. Adam, R. Curci, M. E. González-Núñez, R. Mello, *J. Am. Chem. Soc.* **1991**, 113, 7654.
- 41 R. Mello, L. Cassidei, M. Fiorentino, C. Fusco, R. Curci, *Tetrahedron Lett.* **1990**, 31, 3067.
- 42 D. S. Teager, R. K., Jr. Murray, *J. Org. Chem.* **1993**, 58, 5548.
- 43 D. Kuck, A. Schuster, C. Fusco, M. Fiorentino, R. Curci, *J. Am. Chem. Soc.* **1994**, 116, 2375.
- 44 P. de Macedo Puyau, J. J. Perie, *Synth. Commun.* **1998**, 28, 2679.
- 45 W. Adam, Precht, F. *Chem. Ber.* **1991**, 124, 2369.
- 46 R. Saladino, M. Mezzetti, E. Mincione, I. Torrini, M. P. Paradisi, G. Masteropietro, *J. Org. Chem.* **1999**, 64, 8468.
- 47 R. Curci, A. Detomaso, T. Prencipe, G. B. Carpenter, *J. Am. Chem. Soc.* **1994**, 116, 8112.
- 48 D. Yang, M.-K. Wong, Y.-C. Yip, *J. Org. Chem.* **1995**, 60, 3887.
- 49 M. Frohn, Z.-X. Wang, Y. Shi, *J. Org. Chem.* **1998**, 63, 6425.
- 50 G. Asensio, M. E. González-Núñez, C. Biox Bernadini, R. Mello, W. Adam, *J. Am. Chem. Soc.* **1993**, 115, 7250.
- 51 M. Ferrer, F. Sánchez-Baeza, A. Messeguer, A. Diaz, M. Rubiralta, *J. Chem. Soc., Chem. Commun.* **1995**, 293.

- 52 W. Adam, J. Bialas, L. Hadjirapoglou, *Chem. Ber.* **1991**, 124, 2377.
- 53 R. W. Murray, M. Singh, *Org. Synth. Coll. Vol.* **9** **1998**, 288.
- 54 K. Pramod, P. E. Eaton, R. Gilardi, J. L. Flippen-Anderson, *J. Org. Chem.* **1990**, 55, 6105.

References to Section 2.1.3

- 1 D. J. Hopper, M. R. Jones, M. J. Causer, *FEBS Letters* **1985**, 182, 485.
- 2 I. D. Bossert, G. Whited, D. T. Gibson, L. Y. Young, *J. Bacteriol.* **1989**, 171, 2956.
- 3 O. Kniemeyer, J. Heider, *J. Biol. Chem.* **2001**, 276, 21381.
- 4 H. A. Johnson, D. A. Pelletier, A. M. Spormann, *J. Bacteriol.* **2001**, 183, 4536.
- 5 R. Rabus, M. Kube, A. Beck, F. Widdel, R. Reinhardt, *Arch. Microbiol.* **2002**, 178, 506.
- 6 R. H. H. van den Heuvel, C. Laane, W. J. H. van Berkel, *Adv. Synth. Catal.* **2001**, 343, 515.
- 7 R. H. H. van den Heuvel, M. W. Fraaije, A. Mattevi, C. Laane, W. J. H. van Berkel, *J. Mol. Catal. B. Enzym.* **2001**, 11, 185.
- 8 W. Adam, M. Lazarus, C. R. Saha-Möller, O. Weichold, U. Hoch, D. Häring, P. Schreier, *Adv. Biochem. Eng. Biotechnol.* **1999**, 63, 73.
- 9 M. P. J. van Deurzen, F. van Rantwijk, R. A. Sheldon, *Tetrahedron* **1997**, 53, 13183.
- 10 F. van Rantwijk, R. A. Sheldon, *Curr. Opin. Biotechnol.* **2000**, 11, 554.
- 11 M. P. J. van Deurzen, K. Seelbach, F. van Rantwijk, U. Kragl, R. A. Sheldon, *Biocatal. Biotransf.* **1997**, 15, 1.
- 12 F. van de Velde, N. D. Lourenco, M. Bakker, F. van Rantwijk, R. A. Sheldon, *Biotechnol. Bioeng.* **2000**, 69, 286.
- 13 F. van de Velde, F. van Rantwijk, R. A. Sheldon, *Trends Biotechnol.* **2001**, 19, 73.
- 14 B. Witholt, M.-J. de Smet, J. Kingma, J. B. van Beilen, R. G. Lageveen, G. Eggink, *Trends Biotechnol.* **1990**, 8, 46.
- 15 A. Schmid, J. S. Dordick, B. Hauer, A. Kiener, M. Wubbolts, B. Witholt, *Nature* **2001**, 409, 258.
- 16 D. R. Boyd, N. D. Sharma, C. C. R. Allen, *Curr. Opin. Biotechnol.* **2001**, 12, 564.
- 17 H. L. Holland, *Organic Synthesis with Oxidative Enzymes*, Wiley–VCH. New York, **1992**.
- 18 H. L. Holland, in *Biotransformations 1*, Vol. 8a (Ed.: D. R. Kelly), Wiley–VCH. Weinheim, Germany, **1998**, pp. 475.
- 19 S. L. Flitsch, S. J. Aitken, C. S.-Y. Chow, G. Grogan, A. Staines, *Bioorg. Chem.* **1999**, 27, 81.
- 20 S. W. May, *Curr. Opin. Biotechnol.* **1999**, 10, 370.
- 21 H. L. Holland, *Curr. Opin. Chem. Biol.* **1999**, 3, 22.
- 22 H. L. Holland, H. K. Weber, *Curr. Opin. Biotechnol.* **2000**, 11, 547.
- 23 G. J. Grogan, H. L. Holland, *J. Mol. Catal. B. Enzym.* **2000**, 9, 1.
- 24 H. L. Holland, in *Stereoselective Biocatalysis* (Ed.: R. N. Patel), Marcel Dekker, New York, **2000**, pp. 131.
- 25 R. Azerad, in *Stereoselective Biocatalysis* (Ed.: R. N. Patel), Marcel Dekker, New York, **2000**, pp. 152.
- 26 Z. Li, J. B. van Beilen, W. A. Duetz, A. Schmid, A. de Raadt, H. Griengl, B. Witholt, *Curr. Opin. Chem. Biol.* **2002**, 6, 136.
- 27 S. L. Flitsch, A. Schmid, F. Hollmann, B. Bühler, G. Grogan, K.-H. van Pée, in *Enzyme Catalysis in Organic Synthesis*, Vol. III, 2nd ed. (Eds.: K. Drauz, H. Waldmann), Wiley–VCH. Weinheim, Germany, **2002**, pp. 1065.
- 28 M. D. Mihovilovic, B. Müller, P. Stanetty, *Eur. J. Org. Chem.* **2002**, 1, 3711.
- 29 S. M. Roberts, P. W. H. Wan, *J. Mol. Catal. B. Enzym.* **1998**, 4, 111.
- 30 E. M. Gillam, *Clin. Exp. Pharmacol. P.* **2005**, 32, 147.
- 31 B. Bühler, A. Schmid, *J. Biotechnol.* **2004**, 113, 183.
- 32 Z. Li, D. L. Chang, *Curr. Org. Chem.* **2004**, 8, 1647.
- 33 J. B. van Beilen, W. A. Duetz, A. Schmid, B. Witholt, *Trends Biotechnol.* **2003**, 21, 170.
- 34 J. B. van Beilen, E. G. Funhoff, *Curr. Opin. Biotechnol.* **2005**, 16, in press.

- 35 E. I. Solomon, U. M. Sundaram, T. E. Machonkin, *Chem. Rev.* **1996**, 96, 2563.
- 36 J. P. Klinman, *Chem. Rev.* **1996**, 96, 2541.
- 37 K. Wimalasena, K. R. Alliston, *Biochemistry* **1999**, 38, 14916.
- 38 M. J. Coon, A. H. Connery, R. W. Eastbrook, V. Gelboin, J. R. Gillette, P. J. O'Brien, *Microsomes, Drug Oxidation and Chemical Carcinogens*, Vol. 1 and 2, Academic Press, New York, **1980**.
- 39 F. P. Guengerich, *Mammalian Cytochromes P450*, Vol. 1 and 2, CRC Press, Boca Raton, FL, **1987**.
- 40 P. R. Ortiz de Montellano, *Cytochrome P450 Structure, Mechanism, and Biochemistry*, 2nd ed., Plenum Press, New York, **1995**.
- 41 S. Schneider, M. G. Wubbolts, G. Oesterheld, D. Sanglard, B. Witholt, *Biotechnol. Bioeng.* **1999**, 64, 333.
- 42 S. Schneider, M. G. Wubbolts, D. Sanglard, B. Witholt, *Appl. Environ. Microbiol.* **1998**, 64, 3784.
- 43 V. Urlacher, R. D. Schmid, *Curr. Opin. Biotechnol.* **2002**, 13, 557.
- 44 M. Sono, M. P. Roach, E. D. Coulter, J. H. Dawson, *Chem. Rev.* **1996**, 96, 2841.
- 45 K. G. Ravichandran, S. S. Boddupalli, C. A. Hasermann, J. A. Peterson, J. Deisenhofer, *Science* **1993**, 261, 731.
- 46 A. W. Munro, D. G. Leys, K. J. McLean, K. R. Marshall, T. W. B. Ost, S. Daff, C. S. Miles, S. K. Chapman, D. A. Lysek, C. C. Moser, C. C. Page, P. L. Dutton, *Trends Biochem. Sci.* **2002**, 27, 250.
- 47 M. A. Noble, C. S. Miles, S. K. Chapman, D. A. Lysek, A. C. MacKay, G. A. Reid, R. P. Hanzlik, A. W. Munro, *Biochem. J.* **1999**, 339, 371.
- 48 T. L. Poulos, R. Raag, *FASEB J.* **1992**, 6, 674.
- 49 J. K. Yano, L. S. Koo, D. J. Schuller, H. Li, P. R. Ortiz de Montellano, T. L. Poulos, *J. Biol. Chem.* **2000**, 275, 31086.
- 50 J. K. Yano, F. Blasco, H. Li, R. D. Schmid, A. Henne, T. L. Poulos, *J. Biol. Chem.* **2003**, 278, 608.
- 51 I. Schlichting, J. Berendzen, K. Chu, A. M. Stock, S. A. Maves, D. E. Benson, R. M. Sweet, D. Ringe, G. A. Petsko, S. G. Sligar, *Science* **2000**, 287, 1615.
- 52 M. Newcomb, P. F. Hollenberg, M. J. Coon, *Arch. Biochem. Biophys.* **2003**, 409, 72.
- 53 M. J. Coon, *Annu. Rev. Pharmacol.* **2005**, 45, 1.
- 54 M. J. Coon, *Biochem. Biophys. Res. Com.* **2003**, 312, 163.
- 55 P. Hlavica, *Eur. J. Biochem.* **2004**, 271, 4335.
- 56 A. D. N. Vaz, D. F. McGinnity, M. J. Coon, *Proc. Natl. Acad. Sci. USA* **1998**, 95, 3555.
- 57 M. Newcomb, R. Shen, S.-Y. Choi, P. H. Toy, P. F. Hollenberg, A. D. N. Vaz, M. J. Coon, *J. Am. Chem. Soc.* **2000**, 122, 2677.
- 58 F. Oligaro, N. Harris, S. Cohen, M. Filatov, S. P. de Visser, S. Shaik, *J. Am. Chem. Soc.* **2000**, 122, 8977.
- 59 S. P. de Visser, F. Oligaro, N. Harris, S. Shaik, *J. Am. Chem. Soc.* **2001**, 123, 3037.
- 60 J. T. Groves, Y.-Z. Han, in *Cytochrome P450 Structure, Mechanism, and Biochemistry* (Ed.: P. R. Ortiz de Montellano), Plenum Press, New York, **1995**, pp. 3.
- 61 M. Filatov, N. Harris, S. Shaik, *Angew. Chem. Int. Ed. Engl.* **1999**, 38, 3510.
- 62 M. J. Ryle, R. P. Hausinger, *Curr. Opin. Chem. Biol.* **2002**, 6, 193.
- 63 E. I. Solomon, T. C. Brunold, M. I. Davis, J. N. Kemsley, S.-K. Lee, N. Lehnert, F. Neese, A. J. Skulan, Y.-S. Yang, J. Zhou, *Chem. Rev.* **2000**, 100, 235.
- 64 T. D. H. Bugg, *Tetrahedron* **2003**, 59, 7075.
- 65 C. J. Schofield, Z. Zhang, *Curr. Opin. Struct. Biol.* **1999**, 9, 722.
- 66 A. G. Prescott, M. D. Lloyd, *Nat. Prod. Rep.* **2000**, 17, 367.
- 67 R. P. Hausinger, *Crit. Rev. Biochem. Mol. Biol.* **2004**, 39, 21.
- 68 B. J. Wallar, J. D. Lipscomb, *Chem. Rev.* **1996**, 96, 2625.
- 69 I. J. Higgins, D. J. Best, R. C. Hammond, *Nature* **1980**, 286, 561.
- 70 M. Merkx, D. A. Kopp, M. H. Sazinsky, J. L. Blazyk, J. Müller, S. J. Lippard, *Angew. Chem. Int. Ed. Engl.* **2001**, 40, 2782.

- 71 B. G. Fox, W. A. Froland, J. E. Dege, J. D. Lipscomb, *J. Biol. Chem.* **1989**, 264, 10023.
- 72 B. J. Brazeau, J. D. Lipscomb, *Biochemistry* **2003**, 42, 5618.
- 73 B. J. Wallar, J. D. Lipscomb, *Biochemistry* **2001**, 40, 2220.
- 74 A. C. Rosenzweig, C. A. Frederick, S. J. Lippard, P. Nordlund, *Nature* **1993**, 366, 537.
- 75 E. Elango, R. Radhakrishnan, W. A. Froland, B. J. Wallar, C. A. Earhart, J. D. Lipscomb, D. H. Ohlendorf, *Protein Sci.* **1997**, 6, 556.
- 76 P. Nordlund, B. M. Sjöberg, H. Eklund, *Nature* **1990**, 345, 593.
- 77 Z. Lindqvist, W. Huang, G. Schneider, J. Shanklin, *EMBO J.* **1996**, 15, 4081.
- 78 A. Lombardi, C. M. Summa, S. Geremia, L. Randaccio, V. Pavone, W. F. DeGrado, *Proc. Natl. Acad. Sci. USA* **2000**, 97, 6298.
- 79 B. J. Brazeau, R. N. Austin, C. Tarr, J. T. Groves, J. D. Lipscomb, *J. Am. Chem. Soc.* **2001**, 123, 11831.
- 80 D. A. Kopp, S. J. Lippard, *Curr. Opin. Chem. Biol.* **2002**, 6, 568.
- 81 M. H. Baik, M. Newcomb, R. A. Friesner, S. J. Lippard, *Chem. Rev.* **2003**, 103, 2385.
- 82 S.-K. Lee, J. D. Lipscomb, *Biochemistry* **1999**, 38, 4423.
- 83 B. J. Brazeau, J. D. Lipscomb, *Biochemistry* **2000**, 39, 13503.
- 84 B. D. Dunietz, M. D. Beachy, Y. X. Cao, D. A. Whittington, S. J. Lippard, R. A. Friesner, *J. Am. Chem. Soc.* **2000**, 122, 2828.
- 85 S. S. Stahl, W. A. Francisco, M. Merckx, J. P. Klinman, S. J. Lippard, *J. Biol. Chem.* **2001**, 276, 4549.
- 86 B. F. Gherman, M. H. Baik, S. J. Lippard, R. A. Friesner, *J. Am. Chem. Soc.* **2004**, 126, 2978.
- 87 L. Shu, J. C. Nesheim, K. Kauffmann, E. Münck, J. D. Lipscomb, L. Que, Jr., *Science* **1997**, 275, 515.
- 88 S.-K. Lee, J. C. Nesheim, J. D. Lipscomb, *J. Biol. Chem.* **1993**, 268, 21569.
- 89 L. Que, Jr., *J. Biol. Inorg. Chem.* **2004**, 9, 684.
- 90 M. Newcomb, R. N. Shen, Y. Lu, M. J. Coon, P. F. Hollenberg, D. A. Kopp, S. J. Lippard, *J. Am. Chem. Soc.* **2002**, 124, 6879.
- 91 A. M. Valentine, S. S. Stahl, S. J. Lippard, *J. Am. Chem. Soc.* **1999**, 121, 3876.
- 92 A. Grund, J. Shapiro, M. Fennwald, P. Bacha, J. Leahy, K. Markbreiter, M. Nieder, M. Toepfer, *J. Bacteriol.* **1975**, 123, 546.
- 93 I. E. Staijen, R. Marcionelli, B. Witholt, *J. Bacteriol.* **1999**, 181, 1610.
- 94 J. B. van Beilen, S. Panke, S. Lucchini, A. G. Franchini, M. Röthlisberger, B. Witholt, *Microbiology* **2001**, 147, 1621.
- 95 J. N. Baptist, R. K. Gholson, M. J. Coon, *Biochim. Biophys. Acta* **1963**, 69, 40.
- 96 A. M. Chakrabarty, G. Chou, L. G. Gunsalus, *Proc. Natl. Acad. Sci. USA* **1973**, 70, 1137.
- 97 M. Kok, R. Oldenhuis, M. P. G. van der Linden, P. Raatjes, J. Kingma, P. H. van Lelyveld, B. Witholt, *J. Biol. Chem.* **1989**, 264, 5435.
- 98 J. B. van Beilen, M. G. Wubbolds, B. Witholt, *Biodegradation* **1994**, 5, 161.
- 99 J. A. Peterson, D. Basu, M. J. Coon, *J. Biol. Chem.* **1966**, 241, 5162.
- 100 R. T. Ruettinger, G. R. Griffith, M. J. Coon, *Arch. Biochem. Biophys.* **1977**, 183, 528.
- 101 R. T. Ruettinger, S. T. Olson, R. F. Boyer, M. J. Coon, *Biochem. Biophys. Res. Com.* **1974**, 57, 1011.
- 102 J. B. van Beilen, J. Kingma, B. Witholt, *Enzyme Microb. Technol.* **1994**, 16, 904.
- 103 J. B. van Beilen, T. H. M. Smits, F. F. Roos, T. Brunner, S. B. Balada, M. Rothlisberger, B. Witholt, *J. Bacteriol.* **2005**, 187, 85.
- 104 A. G. Katopodis, K. Wimalasena, J. Lee, S. W. May, *J. Am. Chem. Soc.* **1984**, 106, 7929.
- 105 S. W. May, A. G. Katopodis, *Enzyme Microb. Technol.* **1986**, 8, 17.
- 106 A. G. Katopodis, H. A. Smith, Jr., S. W. May, *J. Am. Chem. Soc.* **1988**, 110, 897.
- 107 H. Fu, M. Newcomb, C.-H. Wong, *J. Am. Chem. Soc.* **1991**, 113, 5878.
- 108 J. B. van Beilen, D. Penninga, B. Witholt, *J. Biol. Chem.* **1992**, 267, 9149.

- 109 J. Shanklin, C. Achim, H. Schmidt, B. G. Fox, E. Münck, *Proc. Natl. Acad. Sci. USA* **1997**, 94, 2981.
- 110 H.-F. Hsu, L. Que, Jr., J. Shanklin, *J. Inorg. Biochem.* **1999**, 74, 168.
- 111 S. J. Lange, L. Que, Jr., *Curr. Opin. Chem. Biol.* **1998**, 2, 159.
- 112 J. Shanklin, E. Whittle, B. G. Fox, *Biochemistry* **1994**, 33, 12787.
- 113 R. N. Austin, H.-K. Chang, G. J. Zylstra, J. T. Groves, *J. Am. Chem. Soc.* **2000**, 122, 11747.
- 114 T. H. M. Smits, M. Röthlisberger, B. Witholt, J. B. van Beilen, *Environ. Microbiol.* **1999**, 1, 307.
- 115 J. B. van Beilen, T. H. M. Smits, L. G. Whyte, S. Schorch, M. Röthlisberger, T. Plaggemeier, K.-H. Engesser, B. Witholt, *Environ. Microbiol.* **2002**, 4, 676.
- 116 L. G. Whyte, T. H. M. Smits, D. Labbé, B. Witholt, C. W. Greer, J. B. van Beilen, *Appl. Environ. Microbiol.* **2002**, 68, 5933.
- 117 T. H. M. Smits, S. B. Ballada, B. Witholt, J. B. van Beilen, *J. Bacteriol.* **2002**, 184, 1733.
- 118 J. B. van Beilen, Z. Li, W. A. Duetz, T. H. M. Smits, B. Witholt, *Oil Gas Sci. Technol.* **2003**, 58, 427.
- 119 D. A. Kunz, P. J. Chapman, *J. Bacteriol.* **1981**, 146, 179.
- 120 M. G. Wubbolts, P. Reuvekamp, B. Witholt, *Enzyme Microb. Technol.* **1994**, 16, 608.
- 121 M. G. Wubbolts, J. Hoven, B. Melgert, B. Witholt, *Enzyme Microb. Technol.* **1994**, 16, 887.
- 122 B. Bühler, A. Schmid, B. Hauer, B. Witholt, *J. Biol. Chem.* **2000**, 275, 10085.
- 123 S. Harayama, M. Rekik, M. Wubbolts, K. Rose, R. A. Leppik, K. N. Timmis, *J. Bacteriol.* **1989**, 171, 5048.
- 124 M. Suzuki, T. Hayakawa, J. P. Shaw, M. Rekik, S. Harayama, *J. Bacteriol.* **1991**, 173, 1690.
- 125 J. P. Shaw, S. Harayama, *J. Ferment. Bioeng.* **1995**, 79, 195.
- 126 M. Wubbolts, Ph.D. thesis, Rijksuniversiteit Groningen (Groningen, The Netherlands), **1994**.
- 127 J. P. Shaw, S. Harayama, *Eur. J. Biochem.* **1992**, 209, 51.
- 128 R. N. Austin, K. Buzzi, E. Kim, G. J. Zylstra, J. T. Groves, *J. Biol. Inorg. Chem.* **2003**, 8, 733.
- 129 J. Shanklin, E. Whittle, *FEBS Lett* **2003**, 545, 188.
- 130 J. Shanklin, E. Whittle, *J. Inorg. Biochem.* **1999**, 74, 50.
- 131 P. Broun, J. Shanklin, E. Whittle, C. Somerville, *Science* **1998**, 282, 1315.
- 132 J. A. Broadwater, E. Whittle, J. Shanklin, *J. Biol. Chem.* **2002**, 277, 15613.
- 133 Y. Jin, J. D. Lipscomb, *J. Biol. Inorg. Chem.* **2001**, 6, 717.
- 134 B. Behrouzian, C. K. Savile, B. Dawson, P. H. Buist, J. Shanklin, *J. Am. Chem. Soc.* **2002**, 124, 3277.
- 135 W. A. Duetz, J. B. van Beilen, B. Witholt, *Curr. Opin. Biotechnol.* **2001**, 12, 419.
- 136 K. Faber, *Biotransformations in Organic Chemistry*, 5th ed., Springer, Berlin, Germany, **2004**.
- 137 U. Schwaneberg, D. Appel, J. Schmitt, R. D. Schmid, *J. Biotechnol.* **2000**, 84, 249.
- 138 F. Hollmann, A. Schmid, E. Steckhan, *Angew. Chem. Int. Ed. Engl.* **2001**, 40, 169.
- 139 F. Zambianchi, P. Pasta, G. Carrea, S. Colonna, N. Gaggero, J. M. Woodley, *Biotechnol. Bioeng.* **2002**, 78, 489.
- 140 F. Hollmann, P. C. Lin, B. Witholt, A. Schmid, *J. Am. Chem. Soc.* **2003**, 125, 8209.
- 141 F. Hollmann, K. Hofstetter, T. Habicher, B. Hauer, A. Schmid, *J. Am. Chem. Soc.* **2005**, 127, 6540.
- 142 T. Plaggemeier, Ph.D. thesis, University of Stuttgart (Stuttgart, Germany), **2000**.
- 143 Z. Li, H. J. Feiten, J. B. van Beilen, W. Duetz, B. Witholt, *Tetrahedron Asymmetry* **1999**, 10, 1323.
- 144 Z. Li, H. J. Feiten, D. L. Chang, W. A. Duetz, J. B. van Beilen, B. Witholt, *J. Org. Chem.* **2001**, 66, 8424.
- 145 D. L. Chang, B. Witholt, Z. Li, *Org. Lett.* **2000**, 2, 3949.
- 146 D. L. Chang, H. J. Feiten, B. Witholt, Z. Li, *Tetrahedron Asymmetry* **2002**, 13, 2141.
- 147 D. L. Chang, H. J. Feiten, K. H. Engesser, J. B. van Beilen, B. Witholt, Z. Li, *Org. Lett.* **2002**, 4, 1859.
- 148 G. Braunegg, A. de Raadt, S. Feichtenhofer, H. Griengl, I. I. Kopper,

- A. Lehmann, H. J. Weber, *Angew. Chem. Int. Ed. Engl.* **1999**, 38, 2763.
- 149 A. de Raadt, H. Griengl, *Curr. Opin. Biotechnol.* **2002**, 13, 537.
 - 150 A. de Raadt, H. Griengl, M. Petsch, P. Plachota, N. Schoo, H. Weber, G. Braunnegg, I. Kopper, M. Kreiner, A. Zeiser, K. Kieslich, *Tetrahedron Asymmetry* **1996**, 7, 467.
 - 151 A. de Raadt, B. Fetz, H. Griengl, M. F. Klingler, I. Kopper, B. Krenn, D. F. Munzer, R. G. Ott, P. Plachota, H. J. Weber, G. Braunnegg, W. Mosler, R. Saf, *Eur. J. Org. Chem.* **2000**, 3835.
 - 152 A. de Raadt, B. Fetz, H. Griengl, M. F. Klingler, B. Krenn, K. Mereiter, D. F. Munzer, P. Plachota, H. Weber, R. Saf, *Tetrahedron* **2001**, 57, 8151.
 - 153 A. de Raadt, H. Griengl, H. Weber, *Chem. Eur. J.* **2001**, 7, 27.
 - 154 M. S. Hemenway, H. F. Olivo, *J. Org. Chem.* **1999**, 64, 6312.
 - 155 A. Bosetti, J. B. van Beilen, H. Preusting, R. G. Lageveen, B. Witholt, *Enzyme Microb. Technol.* **1992**, 14, 702.
 - 156 M. G. Wubbolts, O. Favre-Bulle, B. Witholt, *Biotechnol. Bioeng.* **1996**, 52, 301.
 - 157 J. B. Russell, G. M. Cook, *Microbiol. Rev.* **1995**, 59, 48.
 - 158 P. Phumathon, G. M. Stephens, *Enzyme Microb. Technol.* **1999**, 25, 810.
 - 159 B. Bühler, I. Bollhalder, B. Hauer, B. Witholt, A. Schmid, *Biotechnol. Bioeng.* **2003**, 81, 683.
 - 160 B. Bühler, I. Bollhalder, B. Hauer, B. Witholt, A. Schmid, *Biotechnol. Bioeng.* **2003**, 82, 833.
 - 161 T. Shibasaki, H. Mori, A. Ozaki, *Biosci. Biotech. Biochem.* **2000**, 64, 746.
 - 162 T. Shibasaki, S. Hashimoto, H. Mori, A. Ozaki, *J. Biosci. Bioeng.* **2000**, 90, 522.
 - 163 M. D. Lilly, *J. Chem. Tech. Biotechnol.* **1982**, 32, 162.
 - 164 M. D. Lilly, J. M. Woodley, *J. Ind. Microbiol.* **1996**, 17, 24.
 - 165 P. Nikolova, O. P. Ward, *J. Ind. Microbiol.* **1993**, 12, 76.
 - 166 G. J. Salter, D. B. Kell, *Crit. Rev. Biotechnol.* **1995**, 15, 139.
 - 167 R. D. Schwartz, J. McCoy, *Appl. Environ. Microbiol.* **1977**, 34, 47.
 - 168 M.-J. de Smet, H. Wynberg, B. Witholt, *Appl. Environ. Microbiol.* **1981**, 42, 811.
 - 169 B. Witholt, O. Favre-Bulle, R. Lageveen, J. Kingma, J. B. van Beilen, H. Marvin, H. Preusting, in *Pseudomonas: Molecular Biology and Biotechnology* (Eds.: E. Galli, S. Silver, B. Witholt), ASM Press, Washington, DC, **1992**, pp. 301.
 - 170 A. Schmid, A. Kollmer, R. G. Mathys, B. Witholt, *Extremophiles* **1998**, 2, 249.
 - 171 K. Furuhashi, M. Shintani, M. Takagi, *Appl. Microbiol. Biotechnol.* **1986**, 23, 218.
 - 172 R. León, P. Fernandes, H. M. Pinheiro, J. M. S. Cabral, *Enzyme Microb. Technol.* **1998**, 23, 483.
 - 173 J. M. Woodley, M. D. Lilly, *Chem. Eng. Sci.* **1990**, 45, 2391.
 - 174 K. Kawakami, T. Nakahara, *Biotechnol. Bioeng.* **1994**, 43, 918.
 - 175 K. Faber, *Biotransformations in Organic Chemistry*, 4th ed., Springer, Berlin, Germany, **2000**.
 - 176 P. J. Gerrits, W. F. Willeman, A. J. J. Straathof, J. J. Heijnen, J. Brussee, A. van der Gen, *J. Mol. Catal. B. Enzym.* **2001**, 15, 111.
 - 177 W. F. Willeman, J. P. Gerrits, U. Hanefeld, J. Brussee, A. J. J. Straathof, A. van der Gen, J. J. Heijnen, *Biotechnol. Bioeng.* **2002**, 77, 239.
 - 178 J. B. van Beilen, R. Holtackers, D. Lüscher, U. Bauer, B. Witholt, W. A. Duetz, *Appl. Environ. Microbiol.* **2005**, 71, 1737.
 - 179 A. Liese, K. Seelbach, C. Wandrey, *Industrial Biotransformations*, Wiley-VCH. Weinheim, Germany, **2000**.
 - 180 A. J. J. Straathof, S. Panke, A. Schmid, *Curr. Opin. Biotechnol.* **2002**, 13, 548.
 - 181 A. S. Bommarius, B. R. Reibel, *Biocatalysis – Fundamentals and Applications*, Wiley-VCH. Weinheim, Germany, **2004**.
 - 182 W.-D. Fessner, *Biocatalysis – From Discovery to Application*, Springer Verlag, Berlin, Germany, **2000**.
 - 183 K. Drauz, H. Waldmann, *Enzyme Catalysis in Organic Synthesis*, Vol. 1–3, 2nd ed., Wiley-VCH. Weinheim, Germany, **2002**.
 - 184 A. J. J. Straathof, P. Adlercreutz, *Applied Biocatalysis*, Harwood Academic Publishers, Amsterdam, The Netherlands, **2000**.

- 185 K. Buchholz, V. Kasche, U. T. Bornscheuer, *Biocatalysts and Enzyme Technology*, Wiley-VCH, Weinheim, Germany, **2005**.
- 186 R. B. Silverman, *The Organic Chemistry of Enzyme-Catalyzed Reactions*, Academic Press, San Diego, CA, **2002**.
- 187 J. Nielsen, J. Villadsen, G. Liden, *Bioreaction Engineering Principles*, 2nd ed., Kluwer Academic / Plenum Publishers, New York, **2003**.
- 188 R. N. Patel, *Stereoselective Biocatalysis*, Marcel Dekker, New York, **2000**.
- 189 R. Azerad, in *Asymmetric Oxidation Reactions* (Ed.: T. Katsuki), Oxford Univ. Press, Oxford, UK, **2001**, pp. 181.
- 190 A. L. Demain, J. E. Davies, *Manual of Industrial Microbiology and Biotechnology*, 2nd ed., ASM Press, Washington, DC, **1999**.
- 191 S. Panke, M. Held, M. G. Wubbolts, B. Witholt, A. Schmid, *Biotechnol. Bioeng.* **2002**, *80*, 33.
- 192 A. Schmid, A. Kollmer, B. Sonnleitner, B. Witholt, *Bioproc. Eng.* **1999**, *20*, 91.
- 1 (a) *Methane Conversion by Oxidative Processes*, E.E. Wolf. Ed.; Van Nostrand Reinhold; New York, 1992; (b) *Catalytic Activation and Functionalization of Light Alkanes. Advances and Challenges*, E. G. Derouane ; J. Haber; F. Lemos; F. R. Ribeiro; M. Guisnet Eds.; Nato AS. Series, Kluwer Academic Publishers, Dordrecht, The Netherlands, 1997; (c) "Catalytic Conversion of Methane to More Useful Chemicals and Fuels: a Challenge for the 21st Century." J. H. Lunsford, *Catalysis Today*, **2000**, *63*, 165; (d) "Cooler Chemistry for the 21st Century." R. A. Periana; *C&E News*, **2001**, *79*, 287; (e) *Natural Gas Conversion II*, H.E. Curry-Hyde; R. F. Howe Eds. Elsevier, New York, 1994.
- 2 (a) B. A. Arndtsen, R. G. Bergman, T. A. Mobley, T. H. Peterson, *Acc. Chem. Res.* **1995**, *28*, 154; (b) A. E. Shilov, G. B. Shulpin, *Activation and Catalytic Reactions of Saturated Hydrocarbons in the Presence of Metal Complexes*, 2000; (c) C. G. Jia, T. Kitamura, Y. Fujiwara, *Acc. Chem. Res.* **2001**, *38*, 633; (d) W. D. Jones, *Acc. Chem. Res.* **2003**, *36*, 140; (e) R. H. Crabtree, *J. Chem. Soc., Dalton Trans.* **2001**, *19*, 2437; (f) J. A. Labinger, J. E. Bercaw, *Nature* **2002**, *417*, 507; (g) R. A. Periana, G. Bhalla, W. J. Tenn III, K. J. H. Young, X. Y. Liu, O. Mironov, C. Jones, V. R. Ziatdinov, *J. Mol. Cat. A–Chem.* **2004**, *220*, 7.
- 3 (a) A. E. Shilov, *Activation of Saturated Hydrocarbons by Transition Metal Complexes*, Riedel, Dordrecht, **1984**; (b) A. E. Shilov, G. B. Shul'pin *Chem. Rev.* **1997**, *97*, 2879.
- 4 For example see Ref. [2f] and references therein.
- 5 R. A. Periana, D. J. Taube, S. Gamble, H. Taube, T. Satoh, H. Fujii, *Science* **1998**, *280*, 560.
- 6 R. A. Periana, O. Mironov, D. Taube, G. Bhalla, C. Jones, *Science*, **2003**, *301*, 814.
- 7 (a) Kua J., X. X., Periana R.A., Goddard W.A. III *Organometallics* **2002**, *21*, 511; (b) X. X., Kua J., Periana R.A., Goddard W.A. III *Organometallics* **2003**, *212*, 2057.
- 8 (a) R. A. Periana, D. J. Taube, E. R. Evitt, D. G. Loffler, P. R. Wentcek, *Science*, **1993**, *259*, 340; (b) R. A. Periana, D. J. Taube, E. R. Evitt, D. G. Loffler, P. R. Wentcek, G. Voss, T. Masuda, *Stud. Surf. Sci. Catal.* **1994**, *81*, 533; (c) R. A. Periana. *Adv. Chem. Ser.* **1997**, *253*, 61.
- 9 (a) J. A. Horsley, D. J. Vanderveken, R. A. Periana. *Catalysis Today* **1995**, *23*, 333; (b) T. R. Cundari, L. A. Snyder, A. Yoshikawa. *Journal of Molecular Structure (Theochem)* **1998**, *425*, 13; (c) T. R. Cundari, A. Yoshikawa. *Journal of Computational Chemistry*, **1998**, *19*, 902–911.
- 10 CH₃HgX species is also an intermediate of sulfonation of methane in oleum. See; A. Sen, M. A. Benvenuto, M. Lin, A. C. Huston, N. Basickes. *J. Am. Chem. Soc.* **1994**, *116*, 998–1003.
- 11 Basickes, N.; Hogan, T. E.; Sen, A. *J. Am. Chem. Soc.* **1996**, *118*, 13111–13112.
- 12 C. Jones, D. Taube, V. R. Ziatdinov, R. A. Periana, R. J. Nielsen, J. Oxgaard,

References and Notes to Section 2.1.4

- W. A. Goddard III, *Angew. Chem. Int. Ed.*, **2004**, 43, 4626.
- 13 R. A. Periana, O. Mironov, D. J. Taube, S. Gamble, *Chem. Commun.*, **2002**, 2376
 - 14 (a) M. S. Wickleder, K. Esser, *Zeitschrift fuer Anorganische und Allgemeine Chemie*, **2002**, 62, 8911; b) M. S. Wickleder, O. Buchner, *Zeitschrift fuer Naturforschung, B. Chemical Sciences*, **2001**, 56, 1340.
 - 15 (a) D. H. McDaniel, L. H. Steinert, *J. Am. Chem. Soc.* **1966**, 88, 4826; (b) S. Wasif, *J. Chem. Soc. A*, **1967**, 1, 142; (c) M. A. Hussein, G. M. Iskander, M. M. Nour, S. Wasif, H. M. Zeidan, *J. Chem. Soc., Dalton Trans: Inorg. Chem.*, **1982**, 9, 1645.
 - 16 N. N. Greenwood, A. Earnshaw, *Chemistry of the Elements*, second edition, Butterworth-Heinemann, Oxford, **1997**, p. 782.
 - 17 (a) A. Sen, *Acc. Chem. Res.*, **1998**, 31, 550; (b) Lin, M.; Hogan, T.; Sen, A. *J. Am. Chem. Soc.* **1997**, 6048.
 - 18 M. Muehlhofer, T. Strassner, W. A. Herrmann *Angew. Chem. Int. Ed.* **2002**, 41, 1745.
 - 19 (a) G. A. Olah, A. Molnar, *Hydrocarbon Chemistry* (Wiley, New York, 1995); (b) Lin, M., Sen, A. *Nature*, **1994**, 368, 613; (c) P. J. F. de Rege, J. A. Gladysz, I. T. Horváth, *Adv. Synth. Catal.* **2002**, 344, 1059; (d) C. Jia, T. Kitamura, Y. Fujiwara, *Acc. Chem. Res.*, **2001**, 34, 633.
 - 20 G. V. Nizova, G. B. Shul'pin, G. Suss-Fink, S. Stanislas, *Chem. Commun.* **1998**, 1885.
 - 21 P. M. Reis *et al.*, *Angew. Chem., Int. Ed.* **2003**, 42, 821.
 - 22 Zerella, M.; Mukhopadhyay, S.; Bell, A. T. *Chem. Commun.* **2004**, 1948–1949.
 - 5 P. A. Hooshiyar, H. Niki, *Int. J. Chem. Kinetics* **1995**, 27, 1197–1206; S. M. Aschmann, R. Atkinson, *Int. J. Chem. Kinetics* **1995**, 27, 613–622.
 - 6 A. S. Dneprovskii, D. V. Kuznetsov, E. V. Eliseenkov, B. Fletcher, J. M. Tanko, *J. Org. Chem.* **1998**, 63, 8860–8864.
 - 7 J. C. Corchado, J. Espinosa-Garcia, *J. Chem. Phys.* **1996**, 105, 3152–3159.
 - 8 E. Tschuikow-Roux, D. R. Salomon, *J. Phys. Chem.* **1987**, 91, 699–702; G. A. Russell, J. A. Seetula, R. S. Timonen, D. Gutman, D. F. Nava, *J. Am. Chem. Soc.* **1988**, 110, 3084–3091.
 - 9 J. M. Hoffmann, K. J. Graham, C. F. Rowell, *J. Org. Chem.* **1975**, 40, 3005–3010; E. W. Della, N. J. Head, P. Mallon, J. C. Walton, *J. Am. Chem. Soc.* **1992**, 114, 10730–10738; J. C. Walton, *J. Chem. Soc., Chem. Commun.* **1987**, 1252–1254.
 - 10 D. D. Tanner, R. J. Arhart, E. V. Blackburn, N. C. Das, N. Wada, *J. Am. Chem. Soc.* **1974**, 96, 829–834.
 - 11 F.-D. Kopinke, M. Remmler, H. Mensing, P. Hugo, *J. Phys. Chem.* **1994**, 98, 1171–1175, and references therein.
 - 12 E. S. Huyser, *J. Am. Chem. Soc.* **1960**, 82, 391–393.
 - 13 W. H. Hunter, D. E. Edgar, *J. Am. Chem. Soc.* **1932**, 54, 2025; V. V. Smirnov, V. M. Zelikman, I. P. Beletskaya, E. N. Golubeva, D. S. Tsvetkov, M. M. Levitskii, M. A. Kazankova, *Zhurn. Org. Khim.* **2002**, 38, 962–966.
 - 14 S. Gershuni, N. Itzhak, J. Rabani, *Langmuir* **1999**, 15, 1141–1146; V. V. Smirnov, E. N. Golubeva, O. A. Zagorskaya, S. M. Nevskaya, M. M. Levitskii, V. Y. Zufman, *Kinetics and Catalysis* **2000**, 41, 399–401.
 - 15 J. A. Hawari, S. Davis, P. S. Engel, B. C. Gilbert, D. Griller, *J. Am. Chem. Soc.* **1985**, 107, 4721–4724.
 - 16 I. Tabushi, Y. Aoyama, S. Kojo, Z.-i. Yoshida, *J. Am. Chem. Soc.* **1972**, 94, 1177–1183.
 - 17 F. Minisci, F. Fontana, L. Zhao, S. Banfi, S. Quici, *Tetrahedron Lett.* **1994**, 35, 8033–8036.
 - 18 I. Tabushi, J. Hamuro, R. Oda, *J. Am. Chem. Soc.* **1967**, 89, 7127–7128.

References and Notes to Section 2.2

- 1 J. B. Dumas, *Liebigs Ann.* **1840**, 33, 187–191.
- 2 R. H. Crabtree, *Chem. Rev.* **1995**, 95, 987–1007.
- 3 W. C. Keene, D. J. Jacob, S. M. Fan, *Atmos. Environ.* **1996**, 30, R1–R3.
- 4 J.-J. Wu, C.-N. Hong, *J. Appl. Phys.* **1997**, 81, 3647–3651.

- 19 T. Kojima, R. A. Leising, S. P. Yan, L. J. Que, *J. Am. Chem. Soc.* **1993**, *115*, 11328–11335.
- 20 G. W. Smith, H. D. Williams, *J. Org. Chem.* **1961**, *26*, 2207–2212.
- 21 F. Minisci, F. Fontana, L. Zhao, S. Banfi, S. Quici, *Tetrahedron Lett.* **1994**, *35*, 8033–8036.
- 22 A. Bravo, F. Francesca, G. Fronza, F. Minisci, L. Zhao, *J. Org. Chem.* **1998**, *63*, 254–263.
- 23 L. Liguori, H.-R. Bjørsvik, A. Bravo, F. Fontana, F. Minisci, *Chem. Commun.* **1997**, 1501–1502.
- 24 P. R. Schreiner, O. Lauenstein, E. D. Butova, P. A. Gunchenko, I. V. Kolomitsin, A. Wittkopp, G. Feder, A. A. Fokin, *Chem. Eur. J.* **2001**, *7*, 4996–5003.
- 25 F. Minisci, F. Fontana, F. Recupero, A. Bravo, E. Pagano, C. Rinaldi, M. di Luca, F. Grossi, H.-R. Bjørsvik, *J. Am. Chem. Soc.* **1999**, *121*, 7760–7765.
- 26 A. B. Shtarev, F. Tian, W. R. Dolbier, Jr., B. E. Smart, *J. Am. Chem. Soc.* **1999**, *121*, 7335–7341.
- 27 A. A. Fokin, O. Lauenstein, P. A. Gunchenko, P. R. Schreiner, *J. Am. Chem. Soc.* **2001**, *123*, 1842–1847.
- 28 P. R. Schreiner, O. Lauenstein, I. V. Kolomitsyn, S. Nadi, A. A. Fokin, *Angew. Chem.* **1998**, *110*.
- 29 P. R. Schreiner, O. Lauenstein, E. D. Butova, A. A. Fokin, *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 2786–2788.
- 30 O. Lauenstein, A. A. Fokin, P. R. Schreiner, *Org. Lett.* **2000**, 2201–2204.
- 31 http://www.oc-praktikum.de/versuche_frameset.php?versuch=3015
- 32 C. M. Starks, *Phase-Transfer Catalysis*, Vol. 326, ACS, Washington, **1987**; M. E. Halpern, *Phase-Transfer Catalysis. Mechanisms and Synthesis*, Vol. 659, ACS, Washington, **1996**; M. E. Halpern, *Phase-Transfer Catalysis*, Vol. 659, ACS Symposium Series, **1997**; M. Halpern, Y. Sasson, M. Rabinowitz, *J. Org. Chem.* **1983**, *48*, 1022–1025; M. Rabinowitz, Y. Cohen, M. Halpern, *Angew. Chem.* **1986**, *98*, 958–968.
- 33 E. V. Dehmlow, S. S. Dehmlow, *Phase Transfer Catalysis*, 3 ed., VCH, Weinheim, **1993**.
- 34 D. T. Sawyer, J. L. Roberts, *Acc. Chem. Res.* **1988**, *21*, 469–476.
- 35 E. V. Dehmlow, M. Lissel, *Chem. Ber.* **1978**, *111*, 3873–3878; E. V. Dehmlow, M. Lissel, J. Heider, *Tetrahedron* **1977**, *33*, 363–366.
- 36 J. A. Orvik, *J. Org. Chem.* **1996**, *61*, 4933–4936.
- 37 K. B. Wiberg, *Chem. Rev.* **1955**, *55*, 713–743.
- 38 D. D. Tanner, T. Ochiai, T. Pace, *J. Am. Chem. Soc.* **1975**, *97*, 6162–6165.
- 39 G. H. Aylward, T. J. V. Findlay, *Daten-sammlung Chemie in SI-Einheiten*, 2 ed., VCH, Weinheim, **1986**.
- 40 E. W. Della, N. J. Head, P. Mallon, J. C. Walton, *J. Am. Chem. Soc.* **1992**, *114*, 10730–10738; D. S. Reddy, M. Maggini, J. Tsanaksidis, P. E. Eaton, *Tetrahedron Lett.* **1990**, 805–806.
- 41 T. Kimura, M. Fujita, H. Sohmiya, H. Ando, *Ultrason. Sonochem.* **2002**, *9*, 205–207.
- 42 P. R. Schreiner, A. A. Fokin, O. Lauenstein, Y. Okamoto, T. Wakita, C. Rinderspacher, G. H. Robinson, J. K. Vohs, C. F. Campana, *J. Am. Chem. Soc.* **2002**, *124*, 13348–13349.
- 43 T. L. Axenrod, B.; Bashir-Hashemi, A.; Dave, P. R.; Reddy, D. S., *Magn. Reson. Chem.* **1991**, *29*, 88–91.
- 44 S. Luh, *J. Org. Chem.* **1977**, *42*, 2790.

References and Notes to Section 2.3

- 1 M. Schmittel, A. Burghart, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2551–2589.
- 2 A. A. Fokin, P. R. Schreiner, *Chem. Rev.* **2002**, *102*, 1551–1593.
- 3 D. W. Werst, A. D. Trifunac, *Acc. Chem. Res.* **1998**, *31*, 651–657; F. Gerson, *Acc. Chem. Res.* **1994**, *27*, 63–69.
- 4 I. B. Bersuker, *Chem. Rev.* **2001**, *101*, 1067–1114.
- 5 R. Signorell, M. Sommayilla, F. Merkt, *Chem. Phys. Lett.* **1999**, *312*, 139–148.
- 6 W. Meyer, *J. Chem. Phys.* **1973**, *58*, 1017–1035; M. N. Paddon-Row, D. J. Fox, J. A. Pople, K. N. Houk, D. W. Pratt, *J. Am. Chem. Soc.* **1985**, *107*, 7696–7700; R. F. Frey, E. R. Davidson, *J. Chem. Phys.* **1988**, *88*, 1775–1785.

- 7 A. Ioffe, S. Shaik, *J. Chem. Soc. Perkin Trans.* **21993**, 1461–1473; A. C. Reddy, D. Danovich, A. Ioffe, S. Shaik, *J. Chem. Soc. Perkin Trans.* **21995**, 1525–1539; H. M. Sulzbach, D. Graham, J. C. Stephens, H. F. Schaefer, *Acta Chem. Scand.* **1997**, 51, 547–555; S. D. Wetmore, R. J. Boyd, L. A. Eriksson, A. Laaksonen, *J. Chem. Phys.* **1999**, 110, 12059–12069.
- 8 R. Signorell, M. Sommayavilla, *J. Electron Spectrosc.* **2000**, 108, 169–176.
- 9 H. Zuilhof, J. P. Dinnocenzo, A. C. Reddy, S. Shaik, *J. Phys. Chem.* **1996**, 100, 15774–15784.
- 10 K. Toriyama, K. Nunome, M. Iwasaki, *J. Chem. Phys.* **1982**, 77, 5891–5912; K. Toriyama, M. Okazaki, K. Nunome, K. Matsuura, *Radiat. Phys. Chem.* **1991**, 37, 15–21.
- 11 P. G. Gassman, R. Yamaguchi, *J. Am. Chem. Soc.* **1979**, 101, 1308–1310.
- 12 A. A. Fokin, P. A. Gunchenko, S. A. Peleshanko, P. v. R. Schleyer, P. R. Schreiner, *Eur. J. Org. Chem.* **1999**, 855–860; A. A. Fokin, P. R. Schreiner, P. A. Gunchenko, S. A. Peleshanko, T. E. Shubina, S. D. Isaev, P. V. Tarasenko, N. I. Kulik, H.-M. Schiebel, A. G. Yurchenko, *J. Am. Chem. Soc.* **2000**, 122, 7317–7326.
- 13 A. A. Fokin, T. E. Shubina, P. A. Gunchenko, S. D. Isaev, A. G. Yurchenko, P. R. Schreiner, *J. Am. Chem. Soc.* **2002**, 124, 10718–10727.
- 14 M. Mella, M. Freccero, A. Albini, *Tetrahedron* **1996**, 52, 5533–5548.
- 15 M. Mella, M. Freccero, T. Soldi, E. Fasani, A. Albini, *J. Org. Chem.* **1996**, 61, 1413–1422.
- 16 W. Adam, A. Corma, M. A. Miranda, M.-J. Sabater-Picot, C. Sahin, *J. Am. Chem. Soc.* **1996**, 118, 2380–2386.
- 17 W. Adam, T. Heidenfelder, C. Sahin, *J. Am. Chem. Soc.* **1995**, 117, 9693–9698.
- 18 F. Minisci, F. Fontana, L. Zhao, S. Banfi, S. Quici, *Tetrahedron Lett.* **1994**, 35, 8033–8036.
- 19 F. Recupero, A. Bravo, H.-R. Bjorsvik, F. Fontana, F. Minisci, M. Piredda, *J. Chem. Soc. Perkin Trans.* **21997**, 2399–2405.
- 20 R. Bernardi, R. Galli, F. Minisci, *J. Chem. Soc.* **1968**, 324–325.
- 21 A. A. Fokin, B. A. Tkachenko, T. E. Shubina, P. A. Gunchenko, D. V. Gusev, J. K. Vohs, G. H. Robinson, A. G. Yurchenko, P. R. Schreiner, *Eur. J. Org. Chem.* **2002**, 3844–3849.
- 22 T. E. Shubina, P. A. Gunchenko, A. G. Yurchenko, P. R. Schreiner, E. D. Butova, A. A. Fokin, *Theor. Exp. Chem.* **2002**, 38, 8–14.
- 23 H. J. Schäfer, in *The Chemistry of Alkanes and Cycloalkanes* (Eds.: S. Patai and Z. Rappoport), John Wiley, New York, **1992**, pp. 781–808.
- 24 V. R. Koch, L. L. Miller, *J. Am. Chem. Soc.* **1973**, 95, 8631–8637.
- 25 F. Vincent, R. Tardivel, P. Mison, P. v. R. Schleyer, *Tetrahedron* **1977**, 33, 325–330.

References to Section 2.4.1

- 1 Calvert, J.G. Pitts, J.N. Photochemistry, Wiley, NY, 1966.
- 2 Gunning, H.E. Strauss, O.P. *Adv. Photochem.*, **1963**, 1, 209.
- 3 S.H. Brown and R.H. Crabtree, *Tetrahedron Lett.*, **1987**, 28, 5599.
- 4 R.R. Ferguson, C.G. Boojamra, S.H. Brown, R.H. Crabtree, *Heterocycles*, **1989**, 28, 121.
- 5 S.H. Brown, R.H. Crabtree, *J. Am. Chem. Soc.*, **1989**, 111, 2935; *J. Am. Chem. Soc.*, **1989**, 111, 2946.
- 6 C.A. Muedas, R.R. Ferguson, S.H. Brown, R.H. Crabtree, *J. Amer. Chem. Soc.*, **1991**, 113, 2233.
- 7 (a) D. Michos, C.A. Sassano, P. Krajnik, R.H. Crabtree, *Angew. Chem., Int. Ed. Engl.*, **1993**, 32, 1491; (b) P. Krajnik, R.R. Ferguson, R.H. Crabtree, *New J. Chem.*, **1993**, 17, 559; (c) P. Krajnik, D. Michos, R.H. Crabtree, *New J. Chem.*, **1993**, 17, 805.
- 8 (a) R.R. Ferguson, R.H. Crabtree, *J. Org. Chem.*, **1991**, 56, 5503; (b) R.R. Ferguson, R.H. Crabtree, unpublished data; K.M. Bell, C.A. McDowell, *Can. J. Chem.*, **1961**, 39, 1419, 1424.
- 9 R. Srinivasan, *J. Am. Chem. Soc.*, **1961**, 83, 4923; J. Meinwald, G.W. Smith, *J. Am. Chem. Soc.*, **1967**, 89, 4923.
- 10 G.J. Mains, *Inorg. Chem.*, **1966**, 5, 114.

- 11 H. Cier, *U.S. Pats.*, 2 640 023 (1953); 2 762 768 (1956)
- 12 M.C. Duval, B. Soep, W.H. Breckenbridge, *J. Phys. Chem.*, **1991**, 95, 7145.
- 13 R.H. Crabtree, *Angew. Chem., Int., Ed.*, **1993**, 32, 789.
- 14 L.A. Fowley, J. C. Lee, R. H. Crabtree, P. E. M. Siegbahn, *J. Organomet. Chem.* **1995**, 504, 57.
- 15 Dhamodharan R. Nisha A. Pushkala K. McCarthy TJ *Langmuir*, **2001**, 17, 3368.
- 16 J.V. Crivello, A.M. Carter, *J. Poly. Sci. A.*, **1993**, 31, 2663.
- 17 T. Sakakura, K. Ishida, M. Tanaka, *Chem. Lett.* **1990**, 585–588.
- 18 T. Sakakura, Y. Tokunaga, T. Sodeyama, M. Tanaka, *Chem. Lett.* **1988**, 885–888.
- 19 T. Sakakura, T. Sodeyama, M. Tanaka, *Chem. Lett.* **1988**, 683–684.
- 20 T. Sakakura, F. Abe, M. Tanaka, *Chem. Lett.* **1991**, 297–298.
- 21 T. Sakakura, F. Abe, M. Tanaka, *Chem. Lett.*, **1991**, 359–362.
- 22 T. Sakakura, T. Sodeyama, Y. Tokunaga, M. Tanaka, *Chem. Lett.* **1987**, 2211–2214.
- 23 T. Sakakura, K. Sasaki, Y. Tokunaga, K. Wada, M. Tanaka, *Chem. Lett.* **1988**, 685–688.
- 24 T. Sakakura, Y. Tokunaga, T. Sodeyama, M. Tanaka, *Chem. Lett.* **1987**, 2375–2378.
- 25 T. Sakakura, F. Abe, M. Tanaka, *Chem. Lett.*, **1990**, 583–584.
- 26 M. J. Burk, R. H. Crabtree, *J. Am. Chem. Soc.* **1987**, 109, 8025–8032.
- 27 H. Felkin, T. Fillebeen-Khan, Y. Gault, R. Holmes-Smith, J. Zakrzewsk, *Tetrahedron Lett.*, **1984**, 25, 1279–1282.
- 28 R. H. Crabtree, *Pure Appl. Chem.*, **1995**, 67, 39–45; R. H. Crabtree, *Angew. Chem., Int. Ed. Engl.*, **1993**, 32, 1491–1492.
- 29 S. E. Boyd, L. D. Field, M. G. Partridge, *J. Am. Chem. Soc.* **1994**, 116, 9492–9497.
- 30 G. P. Rosini, W. T. Boese, A. S. Goldman, *J. Am. Chem. Soc.*, **1994**, 116, 9498–9505.
- 31 J.-C. Choi, T. Sakakura, *J. Am. Chem. Soc.* **2003**, 125, 7762–7763.
- 32 (a) T. E. Bitterwolf, W. B. Scallorn, J. T. Bays, C. A. Weiss, J. C. Linehan, J. Franz, R. Poli, *J. Organomet. Chem.*, **2002**, 652, 95–104; (b) J. S. Bridgewater, T. L. Netzel, J. R. Schoonover, S. M. Massick, P. C. Ford, *Inorg. Chem.*, **2001**, 40, 1466–1476; (c) J. S. Bridgewater, B. Lee, S. Bernhard, J. R. Schoonover, P. C. Ford, *Organometallics*, **1997**, 16, 5592–5594; (d) P. C. Ford, T. L. Netzel, C. T. Spillett, D. B. Pourreau, *Pure Appl. Chem.*, **1990**, 62, 1091–1094; (e) C. T. Spillett, P. C. Ford, *J. Am. Chem. Soc.*, **1989**, 111, 1932–1933.
- 33 H. Moriyama, T. Sakakura, A. Yabe, and M. Tanaka, *J. Mol. Catal.*, **1990**, 60, L9–L12.

References and Notes to Section 2.4.2

- 1 A. H. Janowicz, R. G. Bergman, *J. Am. Chem. Soc.* **1982**, 104, 352–354.
- 2 J. K. Hoyano, W. A. G. Graham, *J. Am. Chem. Soc.* **1982**, 104, 3723–3725.
- 3 W. D. Jones, F. J. Feher, *Organometallics* **1983**, 2, 562–563.
- 4 T. Sakakura, T. Sodeyama, K. Sasaki, K. Wada, M. Tanaka, *J. Am. Chem. Soc.* **1990**, 112, 7221–7229.
- 5 T. Sakakura, M. Tanaka, *Chem. Lett.* **1987**, 249–252.
- 6 T. Sakakura, M. Tanaka, *J. Chem. Soc., Chem. Commun.* **1987**, 758–759.
- 7 T. Sakakura, T. Hayashi, M. Tanaka, *Chem. Lett.* **1987**, 859–862.
- 8 T. Sakakura, M. Tanaka, *Chem. Lett.* **1987**, 1113–1116.
- 9 T. Sakakura, K. Sasaki, Y. Tokunaga, K. Wada, M. Tanaka, *Chem. Lett.* **1988**, 155–158.
- 10 T. Sakakura, K. Ishiguro, M. Okano, T. Sako, *Chem. Lett.*, **1997**, 1089–1090.
- 11 T. Sakakura, F. Abe, M. Tanaka, *Chem. Express*, **1990**, 5, 757–760
- 12 M. Tanaka, T. Sakakura, Y. Tokunaga, T. Sodeyama, *Chem. Lett.* **1987**, 2373–2374.
- 13 Y. Tokunaga, T. Sakakura, M. Tanaka, *J. Mol. Catal.* **1989**, 56, 305–314.
- 14 T. Sakakura, T. Sodeyama, M. Tanaka, *New J. Chem.* **1989**, 13, 737–745.
- 15 T. Sakakura, T. Sodeyama, Y. Tokunaga, M. Tanaka, *Chem. Lett.* **1988**, 263–264.
- 16 T. Sakakura, T. Sodeyama, M. Tanaka, *Chem. Ind. (London)* **1988**, 530–531.

- 34 J.-C. Choi, Y. Kobayashi, T. Sakakura, *J. Org. Chem.*, **2001**, 66, 5262–5263.
- 35 T. E. Bitterwolf, D. L. Kline, J. C. Linehan, C. R. Yonker, R. S. Addleman, *Angew. Chem. Int. Ed. Engl.*, **2001**, 40, 2692–2694.
- 36 J.-C. Choi, T. Sakakura, *Organometallics*, **2004**, 23, 3756–3758.
- 37 A. J. Deeming, B. L. Shaw, *J. Chem. Soc. A* **1969**, 597–602.
- 38 R. A. Jones, F. M. Real, G. Wilkinson, A. M. R. Galas, M. B. Hursthouse, K. M. A. Malik, *J. Chem. Soc., Dalton Trans.* **1980**, 511–518.
- 39 J. Browning, P. L. Goggin, R. J. Goodfellow, M. G. Norton, A. J. M. Rattray, B. F. Taylor, J. Mink, *J. Chem. Soc., Dalton Trans.* **1977**, 2061–2067.
- 8 A. G. Griesbeck, A. Henz, J. Hirt, *Synthesis* **1996**, 1261 and references cited therein.
- 9 B. Giese, P. Wettstein, C. Stähelin, F. Barbosa, M. Neuburger, M. Zehnder, P. Wessig, *Angew. Chem., Int. Ed.* **1999**, 38, 2586.
- 10 (a) H. J. Roth, M. H. E. Raie, T. Schrauth, *Arch. Pharm.* **1974**, 307, 584; (b) A. Abdul-Baki, F. Rotter, T. Schrauth, H. J. Roth, *Arch. Pharm.* **1978**, 311, 341; (c) H. J. Roth, H. George, *Arch. Pharm.* **1970**, 303, 725; (d) W. Weigel, S. Schiller, H.-G. Henning, *Tetrahedron* **1997**, 53, 7855; (e) W. Weigel, S. Schiller, G. Reck, H.-G. Henning, *Tetrahedron Lett.* **1993**, 42, 6737; (f) W. Weigel, P. J. Wagner, *J. Am. Chem. Soc.* **1996**, 118, 12858.
- 11 U. Lindemann, D. Wulff-Molder, P. Wessig, *J. Photochem. Photobiol. A. Chemistry* **1998**, 119, 73.
- 12 P. Wessig, J. Schwarz, *Helv. Chim. Acta* **1998**, 81, 1803.
- 13 (a) H.-G. Henning, T. Dietzsch, J. Fuhrmann, *J. Prakt. Chem.* **1981**, 323, 435; (b) H. Haber, H. Buchholz, R. Sukale, H.-G. Henning, *J. Prakt. Chem.* **1985**, 327, 51; (c) K. Walther, U. Kranz, H.-G. Henning, *J. Prakt. Chem.* **1987**, 329, 859.
- 14 P. Wessig, P. Wettstein, B. Giese, M. Neuburger, M. Zehnder, *Helv. Chim. Acta*, **1994**, 77, 829.
- 15 A. Steiner, P. Wessig, K. Polborn, *Helv. Chim. Acta* **1996**, 79, 1843.
- 16 B. Giese, P. Wettstein, C. Stähelin, F. Barbosa, M. Neuburger, M. Zehnder, P. Wessig, *Angew. Chem. Int. Ed.* **1999**, 38, 2586.
- 17 (a) B. Zhou, P. J. Wagner, *J. Am. Chem. Soc.* **1989**, 111, 6796; (b) J. M. Hornback, M. L. Poundstone, B. Vadlamani, S. M. Graham, J. Gabay, S. T. Patton, *J. Org. Chem.* **1988**, 53, 5597; (c) M. Yoshioka, K. Nishizawa, M. Arai, T. Hasegawa, *J. Chem. Soc. Perkin Trans 1*, **1991**, 541.
- 18 (a) U. Lindemann, D. Wulff-Molder, P. Wessig, *Tetrahedron: Asymmetry* **1998**, 9, 4459; (b) A. G. Griesbeck, H. Heckroth, H. Schmickler, *Tetrahedron Lett.* **1999**, 40, 3137.

References and Notes to Section 2.4.3

- 1 R. G. W. Norrish, M. E. S. Appleyard, M. E. S., *J. Chem. Soc.* **1934**, 874.
- 2 N. C. Yang, D.-D. H. Yang, *J. Am. Chem. Soc.* **1958**, 80, 2913.
- 3 (a) P. J. Wagner, *Acc. Chem. Res.* **1971**, 4, 168; (b) P. J. Wagner, *Topics Curr. Chem.* **1976**, 66, 1; (c) P. J. Wagner, *Acc. Chem. Res.* **1989**, 22, 83; (d) P. Wessig, *Regio-selective Photochemical Synthesis of Carbo- and Heterocyclic Compounds: The Norrish Yang Reaction in W. M. Horspool, F. Lenci (Eds) Organic Photochemistry and Photobiology*, 2nd. edn, CR. Press, Boca Raton, **2003**.
- 4 (a) P. Wessig, O. Mühling, *Angew. Chem., Int. Ed.* **2001**, 40, 1064; (b) P. Wessig, O. Mühling, *Helv. Chim. Acta* **2003**, 86, 865; (c) P. Wessig, J. Schwarz, U. Lindemann, M. C. Holthausen, *Synthesis* **2001**, 1258; (d) P. Wessig, C. Glombitza, G. Müller, J. Teubner, *J. Org. Chem.* **2004**, 69, 7582.
- 5 S. D. Feyter, E. W.-G. Diao, A. H. Zewail, *Angew. Chem. Int. Ed.* **2000**, 39, 260.
- 6 L. J. Johnston, J. C. Scaiano, *Chem. Rev.* **1989**, 89, 521.
- 7 P. J. Wagner, P. A. Kelso, A. E. Kemppainen, R. G. Zepp, *J. Am. Chem. Soc.* **1972**, 94, 7500.

- 19 P. Wessig, *Tetrahedron Lett.* **1999**, 40, 5987.
- 20 P. Wessig, J. Schwarz, U. Lindemann, M. C. Holthausen, *Synthesis* **2001**, 1258.

References and Notes to Section 2.4.4

- 1 D. H. R. Barton, J. M. Beaton, L. E. Geller, M. M. Pechet, *J. Am. Chem. Soc.* **1960**, 82, 2640–2641;
D. H. R. Barton, J. M. Beaton, L. E. Geller, M. M. Pechet, *J. Am. Chem. Soc.* **1961**, 83, 4076–4083.
- 2 (a) A. L. Nussbaum, C. H. Robinson, *Tetrahedron* **1962**, 17, 35–59;
(b) D. H. R. Barton, *The use of photochemical reactions in organic synthesis*, in: *Organic Photochemistry*, Vol. 2. Butterworths, **1968**, pp. 1–15; (c) M. Akhtar, *Some recent developments in the photochemistry of organic nitrites and hypohalites* in: *Advances in Photochemistry*, vol. 2. W. A. Noyes, G. S. Hammond, J. N. Pitts, Jr., (Eds.), pages 263–303, Interscience, **1964**; (d) R. H. Hesse, *Barton reaction*: in *Advances in Free Radical Chemistry*, **1969**, 13, 83; (e) Y. L. Chow, *Photochemistry of nitro and nitroso compounds*: in *The Chemistry of Amino, Nitroso, Nitro Compounds and Their Derivatives*, S. Patai, (Ed.), page 241–290, Wiley, **1982**.
- 3 H. Suginome, *Remote functionalization by alkoxyl radicals generated by the photolysis of nitrite esters: The Barton reaction and related reactions of nitrite esters*: in *CRC Handbook of Organic Photochemistry and Photobiology*, 2nd Edition, W. Horspool and F. Lenci (Eds.), pages 10–21–10–16, CRC Press, **2004**.
- 4 D. H. R. Barton, J. M. Beaton, *J. Am. Chem. Soc.*, **1960**, 82, 2641;
D. H. R. Barton, J. M. Beaton, *J. Am. Chem. Soc.*, **1961**, 83, 4083–4089.
- 5 D. H. R. Barton, N. K. J. Basu, M. Day, R. H. Hesse, M. P. Pechet, A. N. Starratt, *J. Chem. Soc. Perkin Trans. 1*, **1975**, 2243–2251.
- 6 R. Kwok, M. E. Wolff, *J. Org. Chem.*, **1963**, 30, 423–428.
- 7 H. Suginome, Y. Nakayama, H. Senboku, *J. Chem. Soc. Perkin Trans. 1*, **1992**, 1837–1842.
- 8 J. R. Hanson, *Tetrahedron*, **1966**, 22, 1701–1708.
- 9 G. H. Hakimelahi, P. –C. Li, A. A. Moosavi-Movahedi, J. Chamani, G. A. Khodarahmi, T. W. Ly, F. Valiyev, M. K. Leong, S. Hakimelahi, K.-S. Shia, I. Chao, *Org. Biomol. Chem.*, **2003**, 1, 2461–2467.
- 10 P. Kabasakarian, E. R. Townley, M. D. Yudis, *J. Am. Chem. Soc.*, **1962**, 84, 2716–2718. 4-Nitroso-5-phenyl-1-pentanol dimer was a single product (18 % yield) reported in this work. In view of the poor material balance of the product and the limited techniques used for the isolation (recrystallization) and characterization (UV intensity at 297 nm, IR, and elemental analysis) of the photolysis products, reaffirmation of this frequently cited results by modern instruments would be desirable.
- 11 H. Suginome, K. Takakuwa, K. Orito, *Chem. Lett.* **1982**, 1357–1360.
- 12 P. Girard, N. Guillot, W. B. Motherwell, P. Potier, *J. Chem. Soc. Chem. Commun.*, **1995**, 2385–2386.
- 13 J. G. Calvert, J. N. Pitts, Jr., *Photochemistry*, pages 480–485, Wiley, New York, **1966**.
- 14 H. Suginome, T. Mizuguchi, S. Honda, T. Masamune, *J. Chem. Soc. Perkin Trans. 1*, **1977**, 927–935.
- 15 P. Kabasakalian, E. R. Townley, *J. Am. Chem. Soc.*, **1962**, 84, 2711–2716.
- 16 K. Heusler, J. Kalvoda, *Angew. Chem. Int. Ed. Engl.* **1964**, 3, 525–538.
- 17 M. Akhtar, M. M. Pechet, *J. Am. Chem. Soc.*, **1964**, 86, 265–268.
- 18 H. Suginome, T. Mizuguchi, T. Masamune, *J. Chem. Soc. Perkin Trans. 1*, **1976**, 2365–2371.
- 19 M. Akhtar, D. H. R. Barton, P. G. Sammes, *J. Am. Chem. Soc.*, **1965**, 87, 4601–4607.
- 20 H. Suginome, *Reaction and synthetic application of oxygen-centered radicals photochemically generated from alkyl hypoiodites*: in *CRC Handbook of Organic Photochemistry and Photobiology*, 2nd Edition, W. Horspool and F. Lenci (Eds.), pages 109–1–109–44 CRC Press **2004**.

- 21 H. Suginome, M. Murakami, T. Masamune, *Chem. Commun.*, **1966**, 343.
- 22 (a) H. Suginome, H. Nakayama, *J. Chem. Soc. Perkin Trans. 1*, **1992**, 1843–1848; (b) H. Suginome, T. Uchida, *J. Chem. Soc. Chem. Comm.*, **1979**, 701–702.
- 23 (a) C. H. Robinson, O. Gnoj, A. Mitchell, E. P. Oliveto, D. H. R. Barton, *Tetrahedron*, **1965**, 21, 743–755; (b) H. Suginome, N. Yonekura, T. Mizuguchi, T. Masamune, *Bull. Chem. Soc. Jpn.*, **1977**, 50, 3010–3013; (c) H. Suginome, N. Maeda, M. Kaji, *J. Chem. Soc. Perkin Trans. 1*, **1982**, 111–116.
- 24 H. Suginome, N. Sato, T. Masamune, *Tetrahedron*, **1971**, 27, 4863–4881.
- 25 M. D. Paredes, R. Alonso, *J. Org. Chem.*, **2000**, 65, 2292–2304.
- 26 (a) A. L. Nussbaum, R. Wayne, E. Yuan, O. Z. Sarre, E. P. Oliveto, *J. Am. Chem. Soc.*, **1965**, 87, 2451–2456; (b) L. Grossi, S. Strazzari, *Chem. Commun.*, **1997**, 917–918.
- 27 R. D. Rieke, N. A. Moore, *J. Org. Chem.*, **1972**, 413–417.
- 28 J.-M. Surzur, M.-P. Bertrand, R. Nougier, *Tetrahedron Lett.*, **1969**, 4197–4200.
- 29 C. Meystre, K. Heusler, J. Kalvoda, P. Wieland, G. Anner, A. Wettstein, *Experientia*, **1961**, 17, 475. C. Meystre, K. Heusler, J. Kalvoda, P. Wieland, G. Anner, A. Wettstein, *Helv. Chim. Acta.*, **1962**, 45, 1317.
- D. K. Böhme, *Int. J. Mass Spectrom. Ion Processes* **1997**, 161, 175–191.
- 5 Y. Zhang, G. Xiong, S. Sheng, W. Yang, *Catal. Today* **2000**, 63, 517–522.
- 6 S. S. Bharadwaj, L. D. Schmidt, *J. Catal.* **1994**, 146, 11–21.
- 7 P. Münster, H. J. Grabke, *Ber. Bunsenges. Phys. Chem.* **1980**, 84, 1068–1071.
- 8 J. R. Rostrup-Nielsen, *J. Catal.* **1972**, 27, 343–356.
- 9 K. G. Pierce, M. A. Barteau, *Surf. Sci.* **1995**, 326, L473–L476.
- 10 M. Yang, G. A. Somorjai, *J. Am. Chem. Soc.* **2004**, 126, 7698–7708.
- 11 J. H. Lunsford, in: L. Guzzi, F. Solymosi, P. Tétényi (Eds) *The Catalytic Conversion of Methane to Oxygenates and Higher Hydrocarbons*, Part A. Adadémiai Kiadó, Budapest, **1992**.
- 12 E. Goos, H. Hippler, K. Hoyermann, B. Jürges, *Phys. Chem. Chem. Phys.* **2002**, 4, 2011–2018.
- 13 H. F. Calcote, *Combust. Flame* **1981**, 42, 215–242.
- 14 A. G. Gaydon, H. G. Wolfhard, *Flames, Their Structure, Radiation and Temperature*, Chapman and Hall, **1979**.
- 15 R. Tadday, A. A. Suvernev, T. Dreier, J. Wolfrum, *Chem. Phys. Lett.* **1997**, 268, 117–124.
- 16 G. A. Somorjai, M. C. Yang, *Top. Catal.* **2003**, 24, 61–72.
- 17 C. Batiot, B. K. Hodnett, *Appl. Catal. A* **1996**, 137, 179–191.
- 18 A. M. Doyle, S. K. Shaikhutdinov, S. D. Jackson, H. J. Freund, *Angew. Chem. Int. Ed.* **2003**, 42, 5240–5243.
- 19 M. Frank, M. Baumer, R. Kuhnemuth, H. J. Freund, *J. Vac. Sci. Technol. A* **2001**, 19, 1497–1501.
- 20 H. J. Freund, J. Libuda, M. Baumer, T. Risse, A. Carlsson, *Chemical Record: an Official Publication of the Chemical Society of Japan* **2003**, 3, 181–200.
- 21 R. T. K. Baker, E. B. Prestridge, R. L. Garten, *J. Catal.* **1979**, 56, 390.
- 22 M. Klimenkov, S. Nepijko, H. Kühlenbeck, M. Bäumer, R. Schlögl, H. J. Freund, *Surf. Sci.* **1997**, 391, 27–36.
- 23 M. M. V. M. Souza, D. A. G. Aranda, M. Schmal, *J. Catal.* **2001**, 204, 498–511.
- 24 T. Wang, C. Lee, L. D. Schmidt, *Surf. Sci.* **1985**, 163, 181–197.

References to Section 2.5

- 1 T. V. Choudhary, E. Aksoylu, D. W. Goodman, *Catal. Rev. – Sci. Eng.* **2003**, 45, 151–203.
- 2 S. B. Derouane-Abd Hamid, J. R. Anderson, I. Schmidt, C. Bouchy, C. J. H. Jacobsen, E. G. Derouane, *Catal. Today* **2000**, 63, 461–469.
- 3 R. P. Muller, D. M. Philipp, W. A. Goddard, *Top. Catal.* **2003**, 23, 81–98.
- 4 D. Schröder, H. Schwarz, D. E. Clemmer, Y. Chen, P. B. Armentrout, V. I. Baranov,

- 25 M. C. Abello, M. F. Gomez, O. Ferretti, *Appl. Catal. A* **2001**, 207, 421–431.
- 26 S. Albrecht, G. Wendt, G. Lippold, A. Admaski, K. Dyrek, *Solid State Ionics* **1997**, 101, 909–914.
- 27 S. Bergh, P. J. Cong, B. Ehnebuske, S. H. Guan, A. Hagemeyer, H. Lin, Y. M. Liu, C. G. Lugmair, H. W. Turner, A. F. Volpe, W. H. Weinberg, L. Woo, J. Zysk, *Top. Catal.* **2003**, 23, 65–79.
- 28 T. Blasco, J. M. L. Nieto, *Appl. Catal. A* **1997**, 157, 117–142.
- 29 K. Chen, S. Xie, A. T. Bell, E. Iglesia, *J. Catal.* **2001**, 198, 232–242.
- 30 P. Concepcion, J. M. L. Nieto, J. Perezpariente, *J. Mol. Catal. A* **1995**, 97, 173–182.
- 31 B. Grzybowska, J. Sloczynski, R. Grabowski, K. Samson, I. Gressel, K. Wcislo, L. Gengembre, Y. Barbaux, *Appl. Catal. A* **2002**, 230, 1–10.
- 32 H. H. Kung, M. C. Kung, *Appl. Catal. A* **1997**, 157, 105–116.
- 33 E. H. Lee, *Catal. Rev.* **1973**, 8, 285–305.
- 34 O. Lezla, E. Bordes, P. Courtine, G. Hecquet, *J. Catal.* **1997**, 170, 346–356.
- 35 P. Moriceau, B. Grzybowska, Y. Barbaux, G. Wrobel, G. Hecquet, *Appl. Catal. A* **1998**, 168, 269–277.
- 36 J. M. L. Nieto, A. Dejoz, M. I. Vazquez, W. Oleary, J. Cunningham, *Catal. Today* **1998**, 40, 215–228.
- 37 B. M. Weckhuysen, R. A. Schoonheydt, *Catal. Today* **1999**, 51, 223–232.
- 38 W. Weiss, D. Zscherpel, R. Schlögl, *Catal. Lett.* **1998**, 52, 215–220.
- 39 Y. S. Yoon, K. Suzuki, T. Hayakawa, S. Hamakawa, T. Shishido, K. Takehira, *Catal. Lett.* **1999**, 59, 165–172.
- 40 N. Magg, J. B. Giorgi, M. M. Frank, B. Immaraporn, T. Schroeder, M. Baumer, H. J. Freund, *J. Am. Chem. Soc.* **2004**, 126, 3616–3626.
- 41 J. D. Burrington, C. T. Kartisek, R. Grasselli, *J. Catal.* **1984**, 87, 363–380.
- 42 S. B. Abd Hamid, D. Othman, N. Abdullah, O. Timpe, S. Knobl, D. Niemeyer, J. Wagner, D. Su, R. Schlögl, *Top. Catal.* **2003**, 24, 87.
- 43 S. Knobl, G. A. Zenkovets, G. N. Kryukova, O. Ovsitser, D. Niemeyer, R. Schlögl, G. Mestl, *J. Catal.* **2003**, 215, 177–187.
- 44 K. D. Chen, S. B. Xie, E. Iglesia, A. T. Bell, *J. Catal.* **2000**, 189, 421–430.
- 45 J. M. Basset, F. Lefebvre, C. Santini, *Coord. Chem. Rev.* **1998**, 180, 1703–1723.
- 46 R. Raja, T. Khimyak, J. M. Thomas, S. Hermans, B. F. G. Johnson, *Angew. Chem. Int. Ed.* **2001**, 40, 4638–4642.
- 47 J. M. Thomas, R. Schlögl, *Angew. Chem.* **1994**, 106, 316–319.
- 48 H. Werner, O. Timpe, D. Herein, Y. Uchida, N. Pfänder, U. Wild, R. Schlögl, *Catal. Lett.* **1997**, 44, 153–163.
- 49 S. Breiter, M. Estenfelder, H. G. Lintz, A. Tenten, H. Hibst, *Appl. Catal. A* **1996**, 134, 81–89.
- 50 A. Dieterle, G. Mestl, J. Jäger, Y. Uchida, H. Hibst, R. Schlögl, *J. Mol. Catal. A* **2001**, 174, 169–185.
- 51 O. Ovsitser, Y. Uchida, G. Mestl, G. Weinberg, A. Blume, J. Jäger, M. Dieterle, H. Hibst, R. Schlögl, *J. Mol. Catal. A* **2002**, 185, 291–303.
- 52 R. K. Grasselli, J. D. Burrington, *Adv. Catal.* **1981**, 30, 133–163.
- 53 D. Schröder, H. Schwarz, In: G. Quinkert, M. V. Kisakürek (Eds) *Reactivity Concepts for Oxidation Catalysis: Spin and Stoichiometry Problems in Dioxygen Activation*, Helvetica Chimica Acta, Zürich, **2001**, pp. 131–156.
- 54 H. Schwarz, D. Schröder, *Pure Appl. Chem.* **2000**, 72, 2319–2332.
- 55 M. Engeser, M. Schlangen, D. Schröder, H. Schwarz, *Organometallics* **2003**, 22, 3933–3943.
- 56 N. Magg, J. B. Giorgi, A. Hammoudeh, T. Schroeder, M. Baumer, H. J. Freund, *J. Phys. Chem. B* **2003**, 107, 9003–9010.
- 57 N. Magg, J. B. Giorgi, T. Schroeder, M. Baumer, H. J. Freund, *J. Phys. Chem. B* **2002**, 106, 8756–8761.
- 58 H. J. Freund, H. Kühlenbeck, V. Staemmler, *Rep. Prog. Phys.* **1996**, 59, 283–347.
- 59 G. Olah, A. Molnar, *Hydrocarbon Chemistry*, Wiley, 2003, pp. 46 ff.

References and Notes to Section 2.6

- 1 (a) Y. Fujiwara, K. Takaki, Y. Taniguchi, *Synlett* **1996**, 591–599; (b) K. Takaki, K. Nakata, Y. Taniguchi, Y. Fujiwara,

- Yuki Gosei *Kagaku Kyokaishi* **1994**, 52, 809–818; (c) C. Jia, T. Kitamura, Y. Fujiwara, *Acc. Chem. Res.* **2001**, 34, 633–639; (d) Y. Fujiwara, C. Jia, *Palladium-Catalyzed Carboxylative Oxidation of Arenes, Alkanes, and Other Hydrocarbons*, in: *Handbook of Organopalladium Chemistry for Organic Synthesis*, E.-i. Negishi (Ed.), pages 2683–2689, John Wiley & Sons, 2002.
- 2 (a) K. Nakata, T. Miyata, T. Jintoku, A. Kitani, Y. Taniguchi, K. Takaki, Y. Fujiwara, *Bull. Chem. Soc. Jpn.* **1993**, 66, 3755–3759; (b) Y. Fujiwara, K. Takaki, J. Watanabe, Y. Uchida, H. Taniguchi, *Chem. Lett.* **1989**, 1687–1688; (c) K. Nakata, J. Watanabe, K. Takaki, Y. Fujiwara, *Chem. Lett.* **1991**, 1437–1438.
 - 3 (a) T. Nishiguchi, K. Nakata, K. Takaki, Y. Fujiwara, *Chem. Lett.* **1992**, 1141–1142; (b) K. Nakata, Y. Yamaoka, T. Miyata, Y. Taniguchi, K. Takaki, Y. Fujiwara, *J. Organomet. Chem.* **1994**, 473, 329–334.
 - 4 Y. Taniguchi, T. Hayashida, H. Shibasaki, D. Piao, T. Kitamura, T. Yamaji, Y. Fujiwara, *Org. Lett.* **1999**, 1, 557–559.
 - 5 (a) M. Asadullah, Y. Taniguchi, T. Kitamura, Y. Fujiwara, *Tetrahedron Lett.* **1999**, 40, 8867–8871; (b) M. Asadullah, Y. Taniguchi, T. Kitamura, Y. Fujiwara, *Applied Catalysis A. General* **2000**, 194–195, 443–453.
 - 6 M. Asadullah, T. Kitamura, Y. Fujiwara, *J. Catalysis* **2000**, 195, 180–186.
 - 7 M. Asadullah, T. Kitamura, Y. Fujiwara, *Angew. Chem. Int. Ed.* **2000**, 39, 2475.
 - 8 T. Kitamura, Y. Ishida, T. Yamaji, Y. Fujiwara, *Bull. Chem. Soc.* **2003**, 76, 1677–1678.
 - 9 T. Hayashida, K. Ito, Y. Taniguchi, T. Kitamura, Y. Fujiwara, *45th Symposium on Organometallic Chemistry, Japan*, Sept. 12 (1998), Tokyo, Abstracts, p. 390.
 - 10 P. M. Reis, J. A. L. Silva, A. F. Palavra, J. J. R. Frausto da Silva, T. Kitamura, Y. Fujiwara, A. J. L. Pombeiro, *Angew. Chem. Int. Ed.* **2003**, 42, 821–823.
 - 1 K. I. Goldberg, A. S. Goldman, Eds. *Activation and Functionalization of C–H Bonds*; American Chemical Society: Washington, DC, 2004; Vol. 885.
 - 2 J. A. Labinger, J. E. Bercaw, *Nature* **2002**, 417, 507.
 - 3 R. H. Crabtree, *J. Chem. Soc., Dalton Trans.* **2001**, 2437.
 - 4 A. E. Shilov, G. B. Shul'pin, *Chem. Rev.* **1997**, 97, 2879.
 - 5 B. A. Arndtsen, R. G. Bergman, T. A. Mobley, T. H. Peterson, *Acc. Chem. Res.* **1995**, 28, 154.
 - 6 C. G. Espino, P. M. Wehn, J. Chow, D. B. J., *J. Am. Chem. Soc.* **2001**, 123, 6935.
 - 7 F. Kakiuchi, S. Murai, *Acc. Chem. Res.* **2002**, 35, 826.
 - 8 N. Chatani, T. Asaumi, S. Yorimitsu, T. Ikeda, F. Kakiuchi, S. Murai, *J. Am. Chem. Soc.* **2001**, 123, 10935.
 - 9 H. M. L. Davies, R. E. J. Beckwith, *Chem. Rev.* **2003**, 103, 2861.
 - 10 J. A. Johnson, D. Sames, *J. Am. Chem. Soc.* **2000**, 122, 6321.
 - 11 B. D. Dangel, J. A. Johnson, D. Sames, *J. Am. Chem. Soc.* **2001**, 123, 8149.
 - 12 J. A. Johnson, N. Li, D. Sames, *J. Am. Chem. Soc.* **2002**, 124, 6900.
 - 13 A. R. Dick, K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2004**, 126, 2300.
 - 14 Y. R. Luo, *Handbook of Bond Dissociation Energies in Organic Compounds*; CR. Press, Boca Raton, 2003.
 - 15 Ethyl sulfonates, carboxylates and phosphates undergo platinum-catalyzed oxidation at the terminal methyl group, but higher analogs react at the omega and omega-1 positions. Lin M., Shen C., Garcia-Zayas E.A., Sen A. *J. Am. Chem. Soc.* **2001**, 123, 1000.
 - 16 T. Ishiyama, N. Miyaoura, *J. Organomet. Chem.* **2003**, 680, 3.
 - 17 T. Ishiyama, N. Miyaoura, *Chem. Rec.* **2004**, 3, 271.
 - 18 H. Chen, S. Schlecht, T. C. Semple, J. F. Hartwig, *Science* **2000**, 287, 1995.
 - 19 T. Ishiyama, J. Takagi, K. Ishida, N. Miyaoura, N. R. Anastasi, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, 124, 390.
 - 20 A. Sen, In: B. Cornils, W. A. Herrmann (Eds) *Applied Homogeneous Catalysis*

- with *Organometallic Compounds*, Vol. 3, 2nd edn, Wiley–VCH, Weinheim, Germany, 2002, p. 1226.
- 21 C. E. Webster, Y. Fan, M. B. Hall, D. Kunz, J. F. Hartwig, *J. Am. Chem. Soc.* **2003**, 125, 858.
 - 22 T. Ishiyama, J. Takagi, J. F. Hartwig, N. Miyauro, *Angew. Chem., Int. Ed.* **2002**, 41, 3056.
 - 23 J. Takagi, K. Sato, J. F. Hartwig, T. Ishiyama, N. Miyauro, *Tetrahedron Lett.* **2002**, 43, 5649.
 - 24 Y. Kondo, D. Garcia-Cuadrado, J. F. Hartwig, N. K. Boen, N. L. Wagner, M. A. Hillmyer, *J. Am. Chem. Soc.* **2002**, 124, 1164.
 - 25 S. Shimada, A. S. Batsanov, J. A. K. Howard, T. B. Marder, *Angew. Chem., Int. Ed.* **2001**, 40, 2168.
 - 26 K. M. Waltz, J. F. Hartwig, *J. Am. Chem. Soc.* **2000**, 122, 11358.
 - 27 W. D. Jones, *Science* **2000**, 287, 1942.
 - 28 W. D. Jones, *Science* **2002**, 295, 289.
 - 29 K. M. Waltz, C. N. Muhoro, J. F. Hartwig, *Organometallics* **1999**, 18, 3383.
 - 30 M. K. Tse, J.-Y. Cho, M. R. Smith, III, *Org. Lett.* **2001**, 3, 2831.
 - 31 R. E. Maleczka, Jr., F. Shi, D. Holmes, M. R. Smith, *J. Am. Chem. Soc.* **2003**, 125, 7792.
 - 32 J.-Y. Cho, M. K. Tse, D. Holmes, R. E. Maleczka, Jr., M. R. Smith, III, *Science* **2002**, 295, 305.
 - 33 C. N. Iverson, M. R. Smith, III, *J. Am. Chem. Soc.* **1999**, 121, 7696.
 - 34 W. H. Lam, Z. Lin, *Organometallics* **2003**, 22, 473.
 - 35 X. Wan, X. Wang, Y. Luo, S. Takami, M. Kubo, A. Miyamoto, *Organometallics* **2002**, 21, 3703.
 - 36 P. V. Ramachandran, H. C. Brown, Editors, *Organoboranes for Syntheses*; A. C. S.: Washington, DC, 2001; Vol. 783.
 - 37 A. Pelter, K. Smith, H. C. Brown, *Borane Reagents*, 1988.
 - 38 P. R. Rablen, J. F. Hartwig, *J. Am. Chem. Soc.* **1996**, 118, 4648.
 - 39 K. M. Waltz, X. He, C. Muhoro, J. F. Hartwig, *J. Am. Chem. Soc.* **1995**, 117, 11357.
 - 40 K. M. Waltz, J. F. Hartwig, *Science* **1997**, 277, 211.
 - 41 H. Chen, J. F. Hartwig, *Angew. Chem., Int. Ed.* **1999**, 38, 3391.
 - 42 K. Kawamura, J. F. Hartwig, *J. Am. Chem. Soc.* **2001**, 123, 8422.
 - 43 G. J. Irvine, M. J. G. Lesley, T. B. Marder, N. C. Norman, C. R. Rice, E. G. Robins, W. R. Roper, G. R. Whittell, L. J. Wright, *Chem. Rev.* **1998**, 98, 2685.
 - 44 D. H. Woodmansee, X. Bu, G. C. Bazan, *Chem. Commun.* **2001**, 619.
 - 45 K. Mertins, A. Zapf, M. Beller, *J. Mol. Catal.* **2004**, 207, 21.
 - 46 T. Ishiyama, K. Ishida, J. Takagi, N. Miyauro, *Chem. Lett.* **2001**, 1082.
 - 47 T. Ishiyama, Y. Nobuta, J. F. Hartwig, N. Miyauro, *Chem. Commun.* **2003**, 2924.
 - 48 J. F. Hartwig, K. S. Cook, M. Hapke, C. D. Incarvito, Y. Fan, C. E. Webster, M. B. Hall, submitted for publication.
 - 49 J. D. Lawrence, M. Takahashi, C. Bae, J. F. Hartwig, in press.
 - 50 W. S. McGivern, A. Derecskei-Kovacs, S. W. North, J. S. Francisco, *J. Phys. Chem.* **2000**, 104, 436.
 - 51 S. J. Blanksby, G. B. Ellison, *Acc. Chem. Res.* **2003**, 36, 255.
 - 52 G. W. Dombrowski, J. P. Dinnocenzo, S. Farid, J. L. Goodman, I. R. Gould, *J. Org. Chem.* **1999**, 64, 427.
 - 53 D. D. M. Wayner, K. B. Clark, A. Rauk, D. Yu, D. A. Armstrong, *J. Am. Chem. Soc.* **1997**, 119, 8925.
 - 54 P. R. Rablen, J. F. Hartwig, S. P. Nolan, *J. Am. Chem. Soc.* **1994**, 116, 4121.
 - 55 C. Bae, J. F. Hartwig, N. K. Boen, R. O. Long, K. S. Anderson, M. A. Hillmyer, in press.

References and Notes to Section 2.8

- 1 *Chem. Eng. News*, **2004**; July 5, Vol. 82, pp. 49–59.
- 2 (a) R. P. O'Connor, E. J. Klein, D. Henning, L. D. Schmidt, *Appl. Catal., A. General* **2003**, 238, 29–40; (b) M. Panizza, C. Resini, G. Busca, E. Fernandez Lopez, V. Sanchez Escrbano, *Catal. Lett.* **2003**, 89, 199–205; (c) F. Patcas, N. Maxim, M. Alifanti, F. Buciuman, *Prog. Catal.* **1999**, 8, 54–60.
- 3 B. M. Weckhuysen, R. A. Schoonheydt, *Catal. Today* **1999**, 51, 223–232.

- 4 G. R. Lappin, L. H. Nemec, J. D. Sauer, J. D. Wagner in: J. I. Kroschwitz, M. Howe-Grant (Eds) *Kirk–Othmer Encyclopedia of Chemical Technology*, 4th edn, Wiley–Interscience, New York, 1996, pp. 839–858.
- 5 R. H. Crabtree, J. M. Mihelcic, J. M. Quirk, *J. Am. Chem. Soc.* **1979**, *101*, 7738–7739.
- 6 (a) R. H. Crabtree, J. M. Quirk, *J. Organomet. Chem.* **1980**, *199*, 99–106; (b) R. H. Crabtree, M. F. Mellea, J. M. Mihelcic, J. M. Quirk, *J. Am. Chem. Soc.* **1982**, *104*, 107–113.
- 7 D. Baudry, M. Ephritikhine, H. Felkin, *J. Chem. Soc., Chem. Commun.* **1980**, 1243–1244.
- 8 D. Baudry, M. Ephritikhine, H. Felkin, J. Zakrzewski, *J. Chem. Soc., Chem. Commun.* **1982**, 1235.
- 9 (a) D. Baudry, M. Ephritikhine, H. Felkin, R. Holmes-Smith, *J. Chem. Soc., Chem. Commun.* **1983**, 788–789; (b) H. Felkin, T. Fillebeen-Khan, Y. Gault, R. Holmes-Smith, J. Zakrzewski, *Tetrahedron Lett.* **1984**, *25*, 1279–1282; (c) H. Felkin, T. Fillebeen-Khan, R. Holmes-Smith, Y. Lin, *Tetrahedron Lett.* **1985**, *26*, 1999–2000.
- 10 M. J. Burk, R. H. Crabtree, C. P. Parnell, R. J. Uriarte, *Organometallics* **1984**, *3*, 816–817.
- 11 M. J. Burk, R. H. Crabtree, *J. Am. Chem. Soc.* **1987**, *109*, 8025–8032.
- 12 T. Fujii, Y. Saito, *J. Chem. Soc., Chem. Commun.* **1990**, 757–758.
- 13 T. Aoki, R. H. Crabtree, *Organometallics* **1993**, *12*, 294–298.
- 14 T. Sakakura, M. Tanaka, *Chem. Lett.* **1987**, 249–252.
- 15 K. Nomura, Y. Saito, *J. Chem. Soc., Chem. Commun.* **1988**, 161.
- 16 T. Sakakura, T. Sodeyama, M. Tokunaga, M. Tanaka, *Chem. Lett.* **1988**, 263–264.
- 17 J. A. Maguire, W. T. Boese, A. S. Goldman, *J. Am. Chem. Soc.* **1989**, *111*, 7088–7093.
- 18 (a) J. A. Maguire, A. S. Goldman, *J. Am. Chem. Soc.* **1991**, *113*, 6706–6708; (b) J. A. Maguire, A. Petrillo, A. S. Goldman, *J. Am. Chem. Soc.* **1992**, *114*, 9492–9498.
- 19 K. Wang, M. E. Goldman, T. J. Emge, A. S. Goldman, *J. Organomet. Chem.* **1996**, *518*, 55–68.
- 20 (a) M. Gupta, C. Hagen, R. J. Flesher, W. C. Kaska, C. M. Jensen, *Chem. Commun.* **1996**, 2083–2084; (b) M. Gupta, C. Hagen, W. C. Kaska, R. E. Cramer, C. M. Jensen, *J. Am. Chem. Soc.* **1997**, *119*, 840–841.
- 21 W. Xu, G. P. Rosini, M. Gupta, C. M. Jensen, W. C. Kaska, K. Krogh-Jespersen, A. S. Goldman, *Chem. Commun.* **1997**, 2273–2274.
- 22 F. Liu, A. S. Goldman, *Chem. Commun.* **1999**, 655–656.
- 23 F. Liu, E. B. Pak, B. Singh, C. M. Jensen, A. S. Goldman, *J. Am. Chem. Soc.* **1999**, *121*, 4086–4087.
- 24 (a) I. Göttker-Schnetmann, P. White, M. Brookhart, *J. Am. Chem. Soc.* **2004**, *126*, 1804–1811; (b) I. Göttker-Schnetmann, M. Brookhart, *J. Am. Chem. Soc.* **2004**, *126*, 9330–9338.
- 25 K. Zhu, P. D. Achord, X. Zhang, K. Krogh-Jespersen, A. S. Goldman, *J. Am. Chem. Soc.* **2004**, *126*, 13044–13053.
- 26 (a) K. B. Renkema, Y. V. Kissin, A. S. Goldman, *J. Am. Chem. Soc.* **2003**, *125*, 7770–7771; (b) A. S. Goldman, K. B. Renkema, M. Czerw, K. Krogh-Jespersen in: K. I. Goldberg, A. S. Goldman (Eds) *Activation and Functionalization of C–H Bonds*, AC. Symposium Series 885, Washington, DC, **2004**, pp. 198–215.
- 27 For a lead reference and a particularly elegant example of the (site-directed) dehydrogenation of an aliphatic group incorporated into a complex organic synthesis see: D. Sames in: K. I. Goldberg, A. S. Goldman (Eds) *Activation and Functionalization of C–H Bonds*, AC. Symposium Series 885, Washington, DC, **2004**, pp. 155–168.
- 28 A. Ray, K. Zhu, Y. V. Kissin, A. E. Cherian, G. W. Coates, A. S. Goldman, *Chem. Commun.* **2005**, in press.
- 29 X.-Q. Gu, W. Chen, D. Morales-Morales, C. M. Jensen, *J. Mol. Catal. A* **2002**, *189*, 119–124.

- 30 X. Zhang, A. Fried, S. Knapp, A. S. Goldman, *Chem. Commun.* **2003**, 2060–2061.
- 31 X. Zhang, A. S. Goldman, to be submitted for publication.
- 32 C. J. Moulton, B. L. Shaw, *J. Chem. Soc., Dalton Trans.* **1976**, 1020–1024.

References to Section 2.9

- 1 For examples of recent reviews on carbenoid induced C–H insertions, see: (a) M. P. Doyle, M. McKervey, T. Ye, *Modern catalytic methods for organic synthesis with diazo compounds: from cyclopropanes to ylides*; John Wiley and Sons, New York, 1998, pp. 112–162; (b) G. A. Sulikowski, K. L. Cha, M. M. Sulikowski, *Tetrahedron: Asymmetry* **1998**, 9, 3145; (c) H. M. L. Davies, R. E. J. Beckwith, *Chem. Rev.* **2003**, 103, 2861.
- 2 J. W. Bode, M. P. Doyle, M. N. Protopopova, Q. -L. Zhou, *J. Org. Chem.* **1996**, 61, 9146.
- 3 M. Anada, S. Hashimoto, *Tetrahedron Lett.* **1998**, 39, 79.
- 4 H. M. L. Davies, T. Hansen, M. R. Churchill, *J. Am. Chem. Soc.* **2000**, 122, 3063.
- 5 Y. Lou, M. Horikawa, R. A. Kloster, N. A. Hawryluk, E. J. Corey, *J. Am. Chem. Soc.* **2004**, 126, 8916.
- 6 (a) M. P. Doyle, L. J. Westrum, W. N. E. Wolthuis, M. M. See, W. P. Boone, V. Bagheri, M. M. Pearson, *J. Am. Chem. Soc.* **1993**, 115, 958; (b) S. Hashimoto, N. Watanabe, M. Anada, S. Ikegami, *J. Synth. Org. Chem. Jpn.* **1996**, 54, 114; (c) D. F. Taber, S. C. Malcolm, *J. Org. Chem.* **1998**, 63, 3717.
- 7 E. Nakamura, N. Yoshikai, M. Yamanaka, *J. Am. Chem. Soc.* **2002**, 124, 7181.
- 8 M. P. Doyle, A. V. Kalinin, *Synlett* **1995**, 1075.
- 9 M. P. Doyle, A. V. Kalinin, *Tetrahedron Lett.* **1996**, 37, 1371.
- 10 N. Watanabe, M. Anada, S. Hashimoto, S. Ikegami, *Synlett* **1994**, 1031.
- 11 M. Anada, S. Hashimoto, *Tetrahedron Lett.* **1998**, 39, 9063.
- 12 T. Takahashi, H. Tsutsui, M. Tamura, S. Kitagaki, M. Nakajima, S. Hashimoto, *Chem. Commun.* **2001**, 1604.
- 13 H. M. L. Davies, M. V. A. Grazini, E. Aouad, *Org. Lett.* **2001**, 3, 1475.
- 14 H. Saito, H. Oishi, S. Kitagaki, S. Nakamura, M. Anada, S. Hashimoto, *Org. Lett.* **2002**, 4, 3887.
- 15 W. Kurosawa, T. Kan, T. Fukuyama, *J. Am. Chem. Soc.* **2003**, 125, 8112.
- 16 A. Demonceau, A. F. Noels, A. J. Hubert, P. Teyssié, *Bull. Soc. Chim. Belg.* **1984**, 93, 945.
- 17 M. M. Diaz-Requejo, T. R. Belderrain, M. C. Nicasio, S. Trofimenko, P. J. Perez, *J. Am. Chem. Soc.* **2002**, 124, 896.
- 18 H. V. R. Dias, R. G. Browning, S. A. Richey, C. J. Lovely, *Organometallics* **2004**, 23, 1200.
- 19 H. M. L. Davies, Q. Jin, P. Ren, A. Y. Kovalevsky, *J. Org. Chem.* **2002**, 67, 4165.
- 20 H. M. L. Davies, Q. Jin, *Tetrahedron: Asymmetry* **2003**, 14, 941.
- 21 H. M. L. Davies, A. M. Walji, R. J. Townsend, *Tetrahedron Lett.* **2002**, 43, 4981.
- 22 H. M. L. Davies, T. M. Gregg, *Tetrahedron Lett.* **2002**, 43, 4951.
- 23 H. M. L. Davies, P. Ren, Q. Jin, *Org. Lett.* **2001**, 3, 3587.
- 24 H. M. L. Davies, P. Ren, *J. Am. Chem. Soc.* **2001**, 123, 2070.
- 25 H. M. L. Davies, R. E. J. Beckwith, E. G. Antoulinakis, Q. Jin, *J. Org. Chem.* **2003**, 68, 6126.
- 26 (a) H. M. L. Davies, T. Hansen, D. W. Hopper, S. A. Panaro, *J. Am. Chem. Soc.* **1999**, 121, 6509; (b) H. M. L. Davies, C. Venkateramani, T. Hansen, D. W. Hopper, *J. Am. Chem. Soc.* **2003**, 125, 6462; (c) J. M. Axten, R. Ivy, L. Krim, J. D. Winkler, *J. Am. Chem. Soc.* **1999**, 121, 6511.
- 27 (a) H. M. L. Davies, D. G. Stafford, T. Hansen, *Org. Lett.* **1999**, 1, 233; (b) H. M. L. Davies, Q. Jin, *Proc. Natl. Acad. Sci., U S A* **2004**, 101, 5472.
- 28 H. M. L. Davies, Q. Jin, *J. Am. Chem. Soc.* **2004**, 126, 10862.

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